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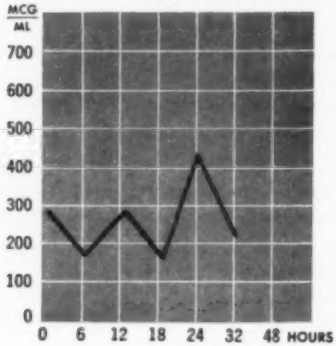

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1. Schoenbach, E. B.; Bryer, M. S., and Long, P. H.: Ann. New York Acad. Sc. 53:245 (Sept. 15) 1950.
2. Welch, H., Hendricks, F. D., Price, C. W., and Randall, W. A.: J. A. Ph. A. (Sc. Ed.) 39:185 (Apr.) 1950.
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MAHLON ASHFORD, *Editor*

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BULLETIN OF
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THE PRESENT STATUS OF ANTIBIOTICS IN BACTERIAL INFECTIONS*

MAXWELL FINLAND

THE introduction and extensive use of sulfanilamide and its derivatives constituted the greatest therapeutic achievement in the field of infectious diseases up to that time. After little more than a decade, however, these drugs have already become overshadowed by the group of antibiotic agents. The extent to which the latter are used is reflected in the volume of their industrial production which now outranks that of all other medicinals. It has been estimated that in 1948 penicillin and streptomycin alone accounted for more than one-half of the total of manufacturer's income from the sale of synthetic drugs. This figure is especially impressive when it is realized that penicillin first became available commercially in 1943 and that streptomycin was not offered for sale until two or three years later.[1] Within the last two years, three additional antibiotics—aureomycin, Chloromycetin(R) and terramycin—have become available and have already become well established and are extensively used. Others like tyrothricin and bacitracin have found

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School, Boston, Mass. Some of the studies referred to in this paper were aided by a grant from the United States Public Health Service.

more limited use, while neomycin and polymyxin, though they are toxic when used systemically and are not officially accepted, may also find some use because of their special range of effectiveness. Furthermore, one may anticipate that the extensive researches still going on in many commercial and other laboratories will bring forth additional agents in the not too distant future, and some of them may also rapidly gain wide acceptance and use.

Since by far the greatest bulk of these agents are used in the therapy and control of bacterial infection, it seems quite clear that it would be futile to attempt to cover the topic assigned within the allotted time, even were an attempt made to do so in the barest outline. It seems more appropriate, therefore, to choose for this presentation some aspect that would embrace many important features of the use of antibiotics and at the same time focus attention on some of the possible implications of their widespread use. For that reason, I have chosen not to discuss the various disease entities which are amenable to each of the various therapeutic agents, nor to delve into the interesting pharmacological aspects or into the many fascinating biochemical problems, nor even to attempt to assess the relative effectiveness of different agents in the diverse infections for which they might be used. Instead I have chosen to begin with a consideration of the various prophylactic uses of the antimicrobial agents. I would also like to bring up the problem of the simultaneous use of multiple agents. And, finally, I would like to call attention to one serious problem with which we are confronted and which may serve as an illustration of the possible implications and consequences of our present day usage of antibacterial therapy.

Prophylactic Uses of Antibacterial Agents

Perhaps the most definitive demonstration of the effectiveness of an antibacterial agent in the prevention of an infectious disease was the virtual eradication of meningococcal infection from certain military units during World War II by the use of sulfadiazine.[2, 3] Not only did new cases of meningitis or other meningococcal infections fail to appear promptly after the use of this drug, but very high meningococcal carrier rates were rapidly reduced, virtually to nil. This was accomplished by the simultaneous oral administration of sulfadiazine to the entire personnel of large, well-circumscribed units either in single doses of one or two grams, or in doses of four grams given over a period of one to

two days. Furthermore, these effects were maintained for an appreciable period after the drug was given and without further administration, except to new arrivals to the units. More sustained effects could be achieved with larger doses or by continuing the prophylactic administration of the drug for somewhat longer periods.

The sulfonamide drugs have been used with some success in the prevention of recurrences of rheumatic fever in individuals who have recently suffered attacks of this disease.[4-6] This has been accomplished either on a clinic basis with the patients remaining in their normal, familial or social environment and also in groups of rheumatic patients kept under close supervision and essentially in isolation, either in special institutions or in rheumatic fever wards. Doses of one to two grams of sulfanilamide, or one gram of sulfadiazine given daily, either in a single or divided doses, have been used either throughout the respiratory season or continuously for one or more years. Some have advocated its use for several years until the patient reaches the age of fifteen or seventeen. In individuals receiving such prophylaxis, group A hemolytic streptococcal infections are markedly reduced in incidence or almost completely eliminated, and the reduction in recurrences of rheumatic fever is attributed to this effect.

It is important here to point out certain basic differences in these two types of prophylaxis. In the case of meningococcal infections, the attempt is made essentially to rid the individual and his environment of the infectious agent. The number of cases of manifest infections is very small indeed and even the number of carriers is relatively small compared to the large number of persons who receive the prophylactic therapy. In other words, in order to insure protection for the entire group, a large number of persons are treated gratis for every case or carrier who actually can be considered a potential source of infection. However, the drug in this instance is used in small doses and for a very brief period, and every person in the exposed population is treated simultaneously. While it is not intended to go into the very important problem of toxicity, it is nevertheless worth mentioning that untoward reactions from such use have been few and relatively unimportant.

The prophylaxis of rheumatic fever involves an attempt to prevent infection in particularly susceptible individuals. In this instance every individual who is treated is essentially a sick person or at least is particularly susceptible, and the prophylaxis is continued presumably as

long as the susceptibility persists. Here the emphasis is on the individual and no attempt is made to change the environment and its potentialities for infecting the individual except perhaps as this might be concerned in those institutions where all of the patients are rheumatics and all are undergoing treatment simultaneously. Because of prolonged use of the agent, the incidence of reactions during rheumatic prophylaxis is likely to be great in terms of the numbers of persons affected, and they might be more serious—even enough to eliminate some individual subjects from further prophylaxis.

In the case of the prophylaxis of meningococcal infections with sulfonamides we are dealing with an organism which is among the more susceptible to these agents. Meningococci that have a high natural resistance to sulfonamides are extremely rare if, indeed, any such strains exist. Most human virulent, group A hemolytic streptococci are highly susceptible to the sulfonamides although resistant strains do occur.

A third type of prophylaxis is exemplified by the use of sulfonamides in bacillary dysentery. In localized outbreaks of this disease, there are usually a large number of patients who are actually sick with the infection, and there is, in addition, a high incidence of carriers who tend to perpetuate it. Entirely apart from hygienic and epidemiologic measures used to reduce the volume of infection in the environment, the sulfonamide drugs have also been employed with varying success in attempts to halt the epidemic spread of bacillary dysentery and to control the carrier state in institutional and other outbreaks.[7, 8] In this instance the drug must be given for longer periods than in the case of prophylaxis of meningococcal infections. Furthermore, the organisms are generally much less susceptible and a higher proportion of failures may be expected. In an occasional outbreak of bacillary dysentery, the sulfonamides have proved completely ineffective due to the resistance of the offending organism.[9] It may be interjected here that although the nonabsorable sulfonamides—such as sulfaguanidine, sulfathalidine, sulfasuxidine—have been used successfully in the control of epidemics, the absorbed drugs, particularly sulfadiazine, have proved more effective in the treatment of this disease and probably also in its prophylactic control.[10]

A fourth type of prophylactic use of antibacterial agents involves attempts to reduce the number of organisms in the contents of the lower bowel prior to surgery of the colon by the oral administration

of poorly absorbed sulfonamides for a few days preoperatively.[11] This type of prophylaxis is applied only to individuals who are given the drug to prevent or minimize serious infectious complications which not infrequently follow some specific and essential surgical operation. This procedure, in various modifications, is now widely used with varying success by most abdominal surgeons.[11]

An entirely different type of prophylaxis is exemplified by the continuous use of sulfadiazine in large military establishments during World War II in an attempt to reduce the incidence of respiratory infections, particularly streptococcal infections and the resulting cases of rheumatic fever.[12, 13] In this instance, either the entire personnel was included or a large segment was given the drug while another was used for controls for special study purposes. Moreover, the drug was given continuously in small doses over long periods. The immediate results were quite favorable and corresponded with what might have been expected from the observations that had already been made in individual rheumatic subjects. Unfortunately, the ultimate results were quite undesirable for, as is now well known, epidemics of streptococcal infections, some of them quite severe and extensive, occurred in several of the units concerned.[14, 15] These were found to be due to sulfonamide-resistant strains of streptococci and the effects of these epidemics might have been considerably more serious had it not been for the fortunate circumstance that penicillin became available at about that time. Furthermore, the prolonged use of the drug under these conditions resulted in an appreciable number of untoward reactions, some of which were quite serious and a few were fatal. In addition, there was no significant reduction of the incidence of scarlet fever or of rheumatic fever in some of these units in which mass prophylaxis with sulfadiazine was practiced, in spite of the fact that there was a definite reduction in other streptococcal infections and also in bacterial pneumonias and in meningococcal infections.

A similar experience was reported on a smaller scale when an attempt was made to prevent acute respiratory infections in an institution for the feebleminded.[16] In this instance although there was a general reduction in incidence of such infection, the continuous use of sulfadiazine gave rise to carrier epidemics of sulfonamide-resistant strains of pneumococci. These strains persisted among the inmates for many months after the administration of the drug was discontinued. Outbreaks of minor

infections occurred during and after the prophylactic period but the relationship between the resistant pneumococci and these infections was uncertain.

The discussion has been limited thus far to the sulfonamide drugs and only a few of the more important examples of their uses as prophylactic agents under diverse circumstances have been mentioned. Needless to say there were many other uses for which the sulfonamides were recommended and in which they were actually used with varying success. Thus the administration of sulfonamide drugs shortly before and after tooth extraction has been advocated as a means of controlling bacteriemia, usually with *Streptococcus viridans*, which follows tooth extraction.[17, 18] This had only limited if any success, and indeed the results are difficult to evaluate. Prophylactic sulfonamides have also been recommended as a means of increasing the safety of tonsillectomies in patients in whom that operation appears to be indicated and on whom it must be performed soon after an acute infection.[19] In such patients they were given for about 24 hours before and for four or five days after the tonsillectomy.

The sulfonamides have also been widely used in attempts to prevent wound infections and have also been given to patients with soft tissue wounds during operations for secondary closure.[20, 21] In the latter circumstance they have been said to reduce the incidence of postclosure infection and delayed healing. The general results of their use for the prevention of infection of soft parts, wounds, compound fractures and burns have on the whole been quite disappointing. This has been particularly true in almost all situations in which sulfonamide drugs were used locally, for example, when they were employed during operations on infected wounds[21] or even during cesarean sections.[22] On the other hand, sulfonamide drugs have been used successfully as prophylactic agents in the prevention of infections following genito-urinary operations.[23]

As soon as penicillin became available in quantity, the fact that it was much less toxic and also much more effective against pathogenic bacteria when compared with the sulfonamides, suggested quite naturally, that it might also prove to be more successful as a prophylactic agent. As a result, this antibiotic has had extensive uses in attempts to prevent or limit infections both in individual patients or in groups of patients for specific purposes, and in large groups of individuals in

attempts to reduce the incidence of infections more generally. Subsequently, each of the more recent antibiotics, in turn, has been or doubtless will be advocated and used in various circumstances for the prevention of specific infections, or in a general way in attempts to eliminate or minimize the occurrence of infection in susceptible individuals or populations.

First of all, it has been shown that penicillin is much more effective than sulfonamides against group A hemolytic streptococci. Penicillin has, therefore, largely replaced the sulfonamide drugs for the prevention of hemolytic streptococcal infection and in the attempts to prevent recrudescences of rheumatic fever, except where the latter drugs are still used for economic reasons. The results reported thus far seem to justify this change and to date, at least, no real indication of the appearance and spread of penicillin-resistant strains of group A hemolytic streptococci has been detected, insofar as available reports indicate. Furthermore, there is evidence that very early treatment of cases of hemolytic streptococcal infection with penicillin, when effective concentrations are maintained for several days, may prevent the development of rheumatic fever or at least minimize its clinical manifestations.[24-26] Toxic effects from the use of penicillin in this manner have been much fewer and less serious than in the case of sulfonamides.

Penicillin is also effective *in vitro* against *Streptococcus viridans* although strains of this organism are much less susceptible to the antibiotic than are the group A hemolytic streptococci. The great majority of cases of subacute bacterial endocarditis which are due to infection with this organism respond favorably to proper treatment with penicillin. It is quite natural, therefore, that this antibiotic has been recommended as the prophylactic agent of choice for use during tooth extractions or during other manipulations in the oral cavity which are known to result in transient bacteremia with *Streptococcus viridans*.[27, 28] Here, the beneficial effects are difficult to gauge, at least with respect to the prevention of subacute bacterial endocarditis in patients with valvular or congenital heart disease and in the prevention of recurrences of subacute bacterial endocarditis in patients who have recovered from this disease following treatment with penicillin. It will require a considerable time and extensive experience to assess this aspect properly.

The story of the very extensive use of sulfonamides in the treatment of gonorrhea, particularly early in the last war, and the subse-

quent change from the very high to the very low incidence of sulfonamide-susceptible gonococci is well known. There are no good reports which adequately reflect the amounts of sulfonamide drugs which may have been used in the prophylaxis of gonorrhea during this period, but it may be surmised that quite extensive amounts were used for that purpose. The subsequent success of penicillin in the treatment of gonorrhea has now been universally attested on the basis of enormous experience and it remains the most effective agent for this disease at the present time. As yet there is no well authenticated evidence for the occurrence or spread of penicillin-resistant strains of gonococci.

Now, there is mounting evidence of the effectiveness of penicillin as a prophylactic agent in gonorrhea.[29] Oral therapy seems to be the only feasible method of administration for large scale prophylaxis, particularly when it is necessarily applied repeatedly in the same individual. Since that route of administration offers some uncertainty in absorption, particularly when it is impossible to control the time of administration in relation to meals, some failures are to be expected. Even so, the reduction in the incidence of gonorrhea in individuals who have taken penicillin prophylactically is quite striking, particularly when a dose of 250,000 units is taken following each exposure. The possibility of dissemination of resistant strains is ever present but has not yet been recognized. Indeed, because of the brief period of each treatment and because of the very high susceptibility of the gonococcus to the antibiotic such an occurrence may not be encountered. In this respect the situation is comparable to that encountered in the case of the sulfonamides and the meningococcus.

The great effectiveness of penicillin as a prophylactic agent in gonococcal infections has also been demonstrated in the case of ophthalmia neonatorum. A single proper instillation of penicillin solution is apparently effective and produces less irritation than that which results from similar use of silver nitrate, the previously accepted prophylactic.[30, 31]

I cannot refrain from calling attention again to the great contrast between the meningococcus and the gonococcus, two organisms which are so closely related biologically, but which differ so strikingly in their relative susceptibility to penicillin and the sulfonamide drugs. The gonococcus is probably the most susceptible organism to penicillin, and no penicillin-resistant strains have been encountered. Most strains

of gonococci are now highly resistant to sulfonamides. On the other hand, the meningococcus is one of the most susceptible organisms to the sulfonamide drugs, as already mentioned, and sulfonamide-resistant meningococci are extremely rare or virtually unknown. The meningococcus is, however, only slightly susceptible to penicillin, resembling in that respect the susceptibility of *Streptococcus viridans* or perhaps the great majority of the staphylococci, and some meningococci are essentially resistant to this antibiotic.

Penicillin is also the treatment of choice in syphilis. In this disease, successful therapy requires prolonged use of large doses. However, a relatively small amount may suffice to abort syphilitic infection in rabbits when administered during the incubation period.[32] The abortive dose given to these animals in a single injection varied with the age of the infection and with the size of the inoculum. Since as Eagle and his co-workers have postulated, the natural disease in man probably involves the inoculation of only a small number of organisms, the infection should be susceptible to abortion by a single dose of penicillin given in a slowly absorbed form or perhaps by mouth.[32] This method has undoubtedly been practiced, purposefully or otherwise, in the course of the prophylaxis of gonorrhea, for, although that is difficult to prove, many cases of syphilis may actually have been prevented in the course of such prophylaxis, particularly with the large doses recently recommended. Direct evidence for the effectiveness of prophylaxis of syphilis, has been obtained in persons known to be exposed to open infection. Complete protection has been obtained with a single visit treatment which included, in addition to penicillin, injections of bismuth and arsenical preparations.[33]

The foregoing already includes examples of prophylaxis where the penicillin is used in individuals and is directed specifically against possible infection with an organism which is known to be sensitive to that antibiotic. A "universal" type of penicillin prophylaxis has more recently been suggested by the demonstration that penicillin may prevent dental caries.[34] This remarkable effect which is attributed to the sensitivity of the lactobacillus to penicillin, has been demonstrated by the use of penicillin solutions in rats and hamsters and by the regular use of a penicillin-containing dentifrice in children, under relatively controlled conditions. It could not be duplicated, however, when a similar dentifrice was used under normal, unregimented conditions.[35] Without

entering into a discussion of the desirability or possible dangers and implications of the use of penicillin dentifrices, one can see here a really universal extension of the use of antibiotics.

Other antibiotics have also been used for specific prophylactic purposes and under special conditions. Thus streptomycin is used during surgical operations on tuberculous patients in the hope of avoiding the spread of infection.[36] Aureomycin has been successfully used during an epidemic of mastitis and breast abscess which occurred among recently delivered mothers in a lying-in hospital and which was proved to be due to a penicillin-resistant strain of *Staphylococcus aureus*.[37] Aureomycin was used not only for the treatment of the mothers, but was also given to the nursing infants in an attempt to eliminate the infections and the staphylococcal carriers among them, who apparently were responsible for perpetuating the epidemic.

In contrast to these uses of antibiotics which are directed specifically against infections with organisms which have either proved to be susceptible or have a high probability of being susceptible to the agent used, there is a host of prophylactic uses which are less specific and where the antibiotics are given in the hope of minimizing or eliminating all types of possible infections that might prove undesirable under special circumstances. Only a few of these need be mentioned in order to illustrate how widely the concept of prophylaxis has permeated general medical management and how far-reaching its effect may be.

Preoperative use of the sulfonamides on large bowel surgery has been extended to include penicillin and streptomycin, in addition.[38] More recently, aureomycin[39, 40] and then Chloromycetin(R)[41] and terramycin[42] have each been advocated for the pre- and postoperative use in abdominal surgery, although some of the reported results of their effects are contradictory. It has been recommended that penicillin be used in large doses in all appendectomy cases to prevent peritonitis.[43] More recently streptomycin has also been added to this regime and the later antibiotics, because of their wider spectrum, have naturally been advocated to supplant or even supplement them.

Genito-urinary surgery offers obvious conditions for postoperative infection. Since a large variety of coliform and occasionally coccal organisms may be involved, the antibiotics are used quite extensively and have largely supplanted the sulfonamides in some clinics as preventives of postoperative urinary tract infection. In obstetrical practice,

patients with prolonged and difficult labor are particularly prone to puerperal infections. In these conditions first the sulfonamides, later penicillin and then streptomycin, aureomycin and other new agents have, in turn, been used with seemingly increasing success.[44] Undoubtedly many obstetricians in their desire to do everything possible to avoid infection have extended this use to all women in labor.

In the surgery of infected or potentially infected wounds or burns the failure of local sulfonamides has stimulated the use of various antibiotics. Here the failure of penicillin in the case of mixed infections has led to the use of bacitracin and tyrothricin as well as all of the new antibiotics as soon as the manufacturers are able to supply them in a convenient form for the purpose at hand, and the licensing authorities have given the green light for their sale.

It has been demonstrated that deaths of animals from excessive total body radiation are associated with dissemination of organisms normally resident in the bowel and the mortality from this type of radiation in such animals may be appreciably reduced by the use of antibiotics directed against these organisms. Aureomycin, terramycin and other antibiotics have proved of prophylactic value in mice.[45, 46] This may, therefore, prove to be a highly important prophylactic use for these and similar agents in persons exposed to excessive radiation, particularly in the event of atomic warfare.

These and many other prophylactic uses of chemotherapy and antibiotics that might be mentioned are not just theoretical suggestions but are actual usages which are practiced in varying degrees by many internists and surgeons and by practitioners of almost every one of the specialties. Each of the uses that have already been mentioned has some justification on the basis of experimental data or from observed clinical experience. One need only mention some of the natural extensions and implications of these uses to realize that the actual prophylactic use of antibiotics entirely apart from their specific indications for the treatment of established infections, is considerably more extensive than that which is implied in the brief list that has already been enumerated. In each instance one can find some theoretical justification but in only a very few indeed has the true value of such uses been proved on the basis of carefully studied and controlled clinical observations.

Thus, the fact that much of the prolonged morbidity from the common cold and influenza in some individuals is associated with a com-

plicating bacterial infection of the upper respiratory tract or with pneumonia, and since most of the complications are due to antibiotic-susceptible bacteria, the "prophylactic" use of such agents in these otherwise mild but very common conditions could be justified. It is only a slight extension of this concept to the idea of treating all persons who might be considered as unusually "susceptible" and from there it is but a short step to include all other people throughout the entire season when respiratory diseases are prevalent,—and perhaps continuously. Such a use in the case of penicillin has indeed been tried and unfortunately has proved to be without any value.[47]

The surgeons may feel justified in extending the prophylactic use of antibiotics to all preoperative and postoperative conditions in order to prevent the development of wound infections or to prevent the spread of established infections. The fervor for such use will be inversely proportional to the skill of the operator and to the care which he normally takes to avoid infection. The internist is likewise wont to employ the agents prophylactically in all types of cases in which complicating infections may seriously hamper the rate or chance of recovery. Thus, all patients with heart disease, particularly those in varying degrees of failure, patients with cerebrovascular accidents, those who are immobilized by neurologic conditions or are in shock or in poor condition due to excessive bleeding, those with obstructive lesions of the urinary tract or of the respiratory passages, those with asthma and hay fever and those who are unconscious from any cause,—indeed, almost any type of patient with a potentially serious illness might be considered a subject for the prophylactic use of antibiotics. The physician may also feel justified in extending prophylactic therapy to all members of the household of any patient whom he is called upon to treat for some definite infection in the hope of preventing them from contracting the same infection. Or he may do so in the hope of preventing them from acquiring infection so that they would not transmit it to a particularly susceptible individual in the household. The industrial physician may feel justified in offering prophylactic antibiotics to all employees in an industry at a time when some of them are ill with infections. He may be particularly impelled to do this under conditions of pressure as might arise during operations in war industries, when there is pressure brought to bear to deliver urgently needed weapons or during the busy season in almost any industry.

Admitted failures from prophylaxis with antibiotics have been encountered, as might be expected from the fact that antibiotics have not been universally or completely successful in the therapy of some established infections, even when the organisms recovered and presumed to be the cause of the infection appear to be susceptible *in vitro*. Thus, it has not been possible by the use of antibiotics to eliminate typhoid bacilli from carriers of that organism.[48] Nor has it been possible to maintain low bacterial counts in the bowel (even should that be considered desirable). Postoperative pulmonary complications have not been prevented by preoperative administration of antibiotics[49] nor have minor respiratory illnesses been reduced by continuous administration of penicillin.[47] Local sulfonamides or even antibiotics have not been too successful in rendering and keeping certain types of wounds and severe burns free of infection. These and some other proved failures are nevertheless quite insignificant beside the many and varied uses for which the antibiotics have been exploited, fully apart from the conditions in which they have been proved to be definitely of therapeutic value—that is in the treatment of infections due to susceptible organisms.

One may summarize the many ancillary and prophylactic uses of antimicrobial agents in terms used by some of our leading politicians as literally offering protection to the individual from the "womb to the tomb." For, is not the mother, and perhaps the unborn child as well, protected by antibiotics during labor? And is not the first gasp of the infant to be followed almost immediately by the instillation of penicillin in the eye? And is not the infant thereafter to receive some antibiotic each time it sniffles, or looks poorly or has a fever? And are not all of his family to be treated to assure his being freed of sources of infection? And is he not to brush his teeth with an antibiotic-containing dentifrice twice daily as long as he lives or has teeth? And so it goes on until his dying day! And then, as he lies dying with his terminal cerebrovascular accident, or heart failure, or even should he be dying from a severe injury, can he be denied the antibiotics that may prevent a secondary pneumonia and thus fail to assure him of an adequate antibiotic concentration in his tissues as he is laid to rest?

Use of Combinations of Antibacterial Agents

The discussion has been concerned thus far primarily with the nontherapeutic uses of antibacterial agents, and the situations that have been

considered have, for the most part, been those in which individual sulfonamides or antibiotics have been recommended or employed to prevent or reduce either specific infections or general groups of infection. Now there has been some evidence that when two or more antibacterial agents are used simultaneously, they may be more effective against certain specific infections than when the same agents are used individually in the same or larger amounts. This evidence has come largely from *in vitro* laboratory investigations but in some instances they have been fortified by results of experiments in animals and even on the basis of limited observations.

I shall not attempt to review the details of the many studies on the combined use of multiple antibacterial agents. Most of them deal with the effects of one or more combinations of drugs on a single organism or at most on a few strains and species of organisms. It is fair to say, however, that there are very few examples indeed of true and marked synergistic action where small and definitely ineffective amounts of agents used in combinations exert striking beneficial or curative effects that are not attainable with much larger amounts of the individual agent when they are used separately. With many combinations, however, the effects have been essentially additive within certain limits. To be sure such additive action may be crucial in the case of agents in which the maximum tolerated dose is below the optimum for the desirable therapeutic effect. Furthermore, in the case of combinations of streptomycin with other agents one of the most significant features that has been emphasized is the delay in emergence of streptomycin-resistant variants. Sometimes the appearance of such variants has actually been prevented when combinations of streptomycin and other drugs have been used.[50]

On the other hand, in the case of many combinations of antibacterial agents there is not even any appreciable additive effect. What is more important, however, is that some combinations have actually proved antagonistic, the favorable effect of one of the agents being reduced or abolished by the addition of another which by itself may be quite active. Price and his coworkers[51] tested combinations of several antibiotics and sulfonamides in order to determine their combined effect on *Salmonella typhosa in vitro* and *in vivo*. They found both increases and decreases in activity among different combinations of these agents as compared with the expected additive effect. With some pairs of

drugs there appeared to be an antagonistic action within certain range of dosage while different amounts of the same agent produced apparently synergistic action. Spicer[52] tested combinations of several antibiotics on a number of species of bacteria and noted four types of effects, namely, synergistic, additive, interfering or indifferent, depending on the combination of drugs for a given strain. Jawetz and his coworkers[53] showed that chloramphenicol interfered with the action of penicillin on many strains of enterococci *in vitro*. They have also demonstrated that any combination of penicillin with chloramphenicol resulted in a much larger number of deaths of mice infected with such streptococci than when the same dose of either drug, particularly penicillin, was used alone.[54]

The use of some of the combinations has already been reported. For example, it has been suggested that streptomycin and aureomycin be added to large doses of penicillin in the treatment of subacute bacterial endocarditis due to streptococci that have failed to respond to penicillin alone.[55] In human and experimental brucellosis, the combination of streptomycin and sulfadiazine appeared to be more effective than either agent alone.[56] In the latter disease, streptomycin is said to increase the effect of aureomycin whereas other combinations of antibiotics have failed to show any enhancing effects.[57, 58] Many other combinations have been advocated and used with success, the more recent of them is illustrated by the addition of para-aminosalicylic acid or of TB1 in the treatment of tuberculosis. The combination of sulfonamides and streptomycin given orally in abdominal surgery is likewise extensively used and advocated. For many of the combinations there is no evidence from *in vitro* studies, from experimental infection or from clinical experience that a beneficial effect could be expected or attained.

Needless to say, the fact that various species of organisms differ in their susceptibility to antibiotics and even different strains of the same species vary in their sensitivity to the same antibiotic has stimulated many physicians to employ multiple agents in the same patients and in many diseases. The demonstration of synergistic or additive effect from combined therapy has further encouraged and stimulated such usage particularly where the response to single agents is expected to be inadequate. With the introduction of increasing numbers of effective agents having varying activities, the number of combinations and permutations becomes appalling. The temptation to use increasing num-

bers of these agents in the therapy of infections is obviously greatest in those cases and in those conditions in which satisfactory results are not obtained with individual agents, but this is also true in infections in which multiple organisms may be operative and particularly in situations in which the causative organisms have not or cannot be isolated or assayed satisfactorily. The possibility that the use of an additional agent may actually vitiate the beneficial effects of others suggests that harm may be done by such usage unless approached with some caution and circumspection. How important the concept of antibiotic antagonism may actually be in practice remains to be determined.

Enough has already been said to emphasize the obvious fact that a major portion of the antibiotics actually administered to individuals may be serving little or no definite purpose in terms of curative effect of active infection. The inordinately large doses of antibiotics used for the treatment of infections with highly susceptible organisms may be included in the same category. For example, in the treatment of gonorrhea or simple hemolytic streptococcal infections or uncomplicated pneumococcal pneumonia with penicillin, only very small amounts are required for the optimum effect. In many hospitals, even in some of the better teaching institutions where the use of most of the agents is under some measure of intelligent control, it has been estimated that less than 10 per cent of the amounts of antibiotics administered is indicated for the optimum curative effect of susceptible infections, even after liberal dosages are allowed for infections in which there are well established indications.

Some Possible Biological Implications with Especial Reference to the Occurrence of Antibiotic-Resistant Staphylococcal Infections: Only indirect mention has been made concerning possible harmful effects. The problem of toxic manifestations and the opportunity for sensitization from the use of antibiotics are probably proportional to the extent to which they are employed. The emergence and spread of sulfonamide-resistant variants is well exemplified in the case of the gonococcus and in that instance may be considered as resulting from the extensive uses of the agents therapeutically. The epidemic spread of sulfadiazine-resistant streptococci in military units may be considered to be a consequence of widespread prophylactic usage. The eventual importance of the emergence of streptomycin-resistant variants during the therapeutic or prophylactic use of that agent is difficult to assess

TABLE I—SENSITIVITY OF STAPHYLOCOCCUS AUREUS TO 4 ANTIBIOTICS

ORGANISMS ISOLATED IN PURE CULTURE OR AS THE PREDOMINANT ONES FROM 50 OF 166 CONSECUTIVE AUTOPSIES AT THE BOSTON CITY HOSPITAL — SPRING 1950

Minimum Inhibiting Concentration µg/ml.	*Penicillin*	*Aureomycin*		*Chloromycetin* (a)	*Terramycin*	
	48 hours	*24 hours*	*48 hours*	*48 hours*	*24 hours*	*48 hours*
<12.5	7(4)	31	0	7	33	26
12.5-25	1	2	11	32	0	3
50-100	3	4	20	11	1	2
200-400	4(1)	13	16	0	4	2
800 or more	35(3)	0	3	0	12	17

Penicillin was used in 42 cases, with aureomycin in 3, with terramycin in 1. The 8 patients who had not received penicillin are noted in parentheses. The sensitivity was tested by an agar plate-dilution method.

aside from the fact that the individual concerned may not derive any benefit from the use of streptomycin in the treatment of his infection. These and many other undesirable effects, including the economic implications of the problems raised, will not be considered further.

The remainder of this presentation will be devoted to one particular problem which has recently become of increasing importance and which may be, at least in part, a consequence of the extensive use of penicillin and other antibiotics. It may be merely one example of the general problem related to the change in bacterial flora during antibiotic therapy. I refer to the increasing number and significance of staphylococcal infections at the Boston City Hospital.

This problem has manifested itself in several ways. From the purely laboratory aspect, hemolytic, coagulase positive strains of *Staphylococcus aureus* have been encountered with increasing frequency in cultures from materials from the respiratory tract and from other sources in patients under treatment with antibiotics. In the majority of cases this has not been reflected in any clinical manifestations of significance; the causative agent of the original infection is promptly eliminated and the infections for which the patients were treated continued to progress favorably. In others, however, these staphylococci were associated with the occurrence of grossly purulent sputum in increasing amounts and there was evidence from physical and x-ray

examination of extending broncho-pulmonary infection. Bacteriemia has also been demonstrated in some of these patients.

In addition, there has been an increasing proportion of penicillin-resistant staphylococci in cultures obtained from all sources, both from obviously infected foci, and from routine nasopharyngeal and sputum cultures. This has already been noted by workers in Great Britain, Australia and in this country.[59] At the Boston City Hospital a marked increase was noted in the penicillin-resistance of strains isolated during 1948 and 1949 as compared with those isolated before 1946.[60] Among those isolated during the past year there has been a preponderance of strains with still greater resistance.

Some of the staphylococci isolated during antibiotic therapy were associated with unusual manifestations of infection with this organism. For example, in three patients under treatment for pertussis or diphtheria with some of the new antibiotics, Chang and Jackson have noted that the rapid disappearance of *Hemophilus pertussis* and *Corynebacterium diphtheriae,* respectively, from the nasopharyngeal cultures was promptly followed by the development of typical scarlet fever. Pharyngeal swabs in these patients have shown pure cultures of hemolytic *Staphylococcus aureus* and no hemolytic streptococci. Staphylococcal scarlet fever was also observed in a patient receiving prophylactic penicillin for an extensive burn, the organism being obtained from the throat and the surface burn in that case.

We have recently encountered what apparently is a new disease entity, namely, staphylococcal dysentery. In several patients under treatment with aureomycin and terramycin, severe diarrhea has been encountered in which the stools have shown pus and blood, and the cultures from these stools have yielded coagulase positive, hemolytic *Staphylococcus aureus* as the predominant organism and occasionally as the only organism which could be cultivated on the surface of blood agar plates. In one of these patients the staphylococcus was also obtained from the blood. Gram stained smears made directly from the liquid stools of some of these patients have shown only the gram-positive cocci and no gram-negative rods. Some of the patients in whom this was observed recently were being treated with terramycin for salmonella infections; in such cases staphylococci rapidly replaced the salmonella in the stools.

In this connection it is of particular interest to note that when terra-

mycin was first made available to us and before any of the patients had been treated with the agent, only a relatively small proportion of staphylococci isolated from active infections were found to be susceptible to that agent.[61] A large proportion of the staphylococci could be considered totally resistant to terramycin. Also following the use of this agent, we have noted the occurrence of staphyloccoci as the predominant or only organism in the urine of some of the patients with chronic or recurrent urinary tract infection.[62]

Finally, staphylococci are being encountered with increasing frequency in the bacteriological studies being carried out in the routine autopsy material by our colleagues at the Mallory Institute of Pathology. Hemolytic *Staphylococcus aureus,* coagulase positive, has been recovered as the only or predominant organism in lungs, blood and other organs in an increasing proportion of the autopsies. Frequently, but not always, there have been changes in the tissues consistent with infection by the staphylococcus. Moreover, as shown in Table I, most of the organisms have proved highly resistant to penicillin and a large proportion of them have been resistant to aureomycin and terramycin. Chloramphenicol has been used only rarely in this hospital and this may explain the relatively low proportion of chloramphenicol-resistant strains.

It is difficult, of course, to say whether these phenomena are a consequence of the widespread use of antibiotics or are merely a coincidence and represent a temporary and transient increase in the appearance of staphylococcal infections such as has been encountered in the past, as for example, during the influenza epidemic of 1940.[63] It seems difficult, from the data at hand, to escape the conclusion that the widespread use of antibiotics is largely responsible for these occurrences.

It must seem rather incongruous that a paper dealing with present status of antibiotic therapy of bacterial infections should fail to devote the major attention to the miraculous results which have been achieved in the cure or amelioration of such a large number of important infectious diseases. Although the temptation was great to discuss and compare details of the applications of individual antibiotics to the treatment of isolated cases or unusual diseases, it seemed more pertinent here to view some of the broader aspects and possible implications of the extensions of the accepted therapeutic usages. Obviously, much further thought and study will have to be devoted to these aspects.

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PRESENT STATUS OF ANTIBIOTIC THERAPY IN VIRAL AND RICKETTSIAL DISEASE*

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WE will begin with a discussion of the rickettsial diseases of man even though these are of appreciably less medical importance in New York and in the United States than are the viral diseases. Within the past three years the problem of the treatment of the rickettsial diseases has been solved. When one speaks of the recent advances and the present status of the therapeutic control of these infections, he speaks of the use of the antibiotics chloramphenicol, aureomycin and terramycin. While this subject is relatively new, several rather complete reviews have already been published.[1,2] Therefore, it will not be necessary at this time to recount the amazing story of the successful search for these substances, the extensive laboratory experience which foretold the efficacy of these drugs in patients, nor the details of the early clinical trials.

In discussing the rickettsioses, it appears preferable to select one of these formerly notorious diseases and to summarize the present information about its treatment. This is feasible because the rickettsial group of agents, and the illnesses which they induce, are similarly affected by the three new antibiotics which have now come into wide usage. Those instances in which minor differences are encountered in the therapy of the diseases will be disposed of briefly.

Scrub typhus will be taken as the illustrative example of the present status of the treatment of rickettsial infections. There are several reasons for this. While not the first of the rickettsioses to be subjected to the newer antibiotics, it was the first in which one of the newer methods of treatment was carefully evaluated. Furthermore, it remains the rickettsial disease which has been most extensively studied by a single group of investigators, hence, the observations of this group on the comparative efficacy of the different antibiotics are of particular

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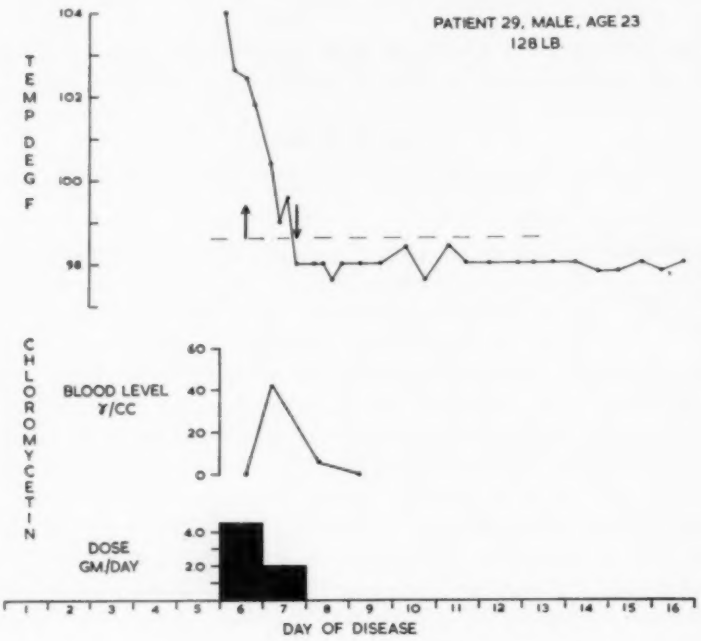

RASH				++	+	○									
ESCHAR	+	+	+	+	±	○									
WF OX-K				80											320
RICKETTSEMIA		+	+	+	○										

Figure 1—Clinical course of scrub typhus in a Malayan treated with chloramphenicol. (Reproduced by permission of the Journal of Clinical Investigation, 1949, *28*:1202.)

value. Finally, my own observations in this field have been more closely associated with scrub typhus than with the other rickettsial diseases.

Figure 1 illustrates the clinical course of disease in a Malayan patient with scrub typhus who was treated with chloramphenicol. A total of about 6.0 grams of drug was administered orally over a period of 24 hours. Before the end of this course of antibiotic, the patient was afebrile and markedly improved. Convalescence was uneventful.

TABLE 1—SCRUB TYPHUS PATIENTS TREATED WITH CHLORAMPENICOL, AUREOMYCIN, TERRAMYCIN OR PARA-AMINOBENZOIC ACID

Therapy	*No. of Patients*	*Average Duration of Fever after Treatment (hrs.)*	*Fatalities*
Chloramphenicol	100	31	0
Aureomycin	29	25	0
Terramycin	7	47	0
Paba	15	89	0
		Duration of Disease	
None	19	17 Days	1

Table 1 summarizes the three year collaborative experience of the U. S. Army Medical Research Units and the members of the Institute for Medical Research in the treatment of patients with scrub typhus.[3] One hundred of these received chloramphenicol; the average duration of their fever after beginning therapy was thirty-one hours. Twenty-nine patients were treated with aureomycin and they became afebrile after twenty-five hours. Seven other patients were treated with terramycin and their fever persisted on the average for forty-seven hours. The figure also contains information on the results obtained in fifteen patients who were treated with para-aminobenzoic acid; here almost ninety hours elapsed from the time the drug was started until the patients were fever free. During the course of these studies in Malaya, there were nineteen patients with scrub typhus who received only symptomatic treatment. These were cared for at a time when specific therapy was not available or else were first seen late in their illness at a time when they did not appear dangerously sick. It may be noted that the average duration of fever in these nineteen control patients was seventeen days. No deaths occurred among the 151 treated cases while one of the nineteen controls succumbed with scrub typhus. The mortality in this disease, in untreated patients, varies considerably in different geographic areas. In Malaya, where these studies were made, the mortality is about 5 per cent.

Such data as those provided in Table 1 clearly show that the three new antibiotics, namely, chloramphenicol, aureomycin and terramycin, are far superior to para-aminobenzoic acid, which was the only useful specific remedy available prior to the advent of chloramphenicol. The

therapeutic effects of aureomycin in patients with scrub typhus are as excellent as those obtained with chloramphenicol. Certain of the patients who received terramycin responded as well as would have been expected had they been given either chloramphenicol or aureomycin. However, a few of those who received terramycin were a little slow in responding and these raised the average febrile period for the group to forty-odd hours.

The Malayan experience revealed practically no serious side effects attributable to the use of chloramphenicol in patients with scrub typhus. While no serious untoward manifestations were exhibited by those persons who were given aureomycin, about 20 per cent of them had annoying gastrointestinal irritation; however, in no instance was it necessary to discontinue aureomycin because of these side effects. In contrast the incidence of nausea and vomiting in the Malayan patients who received terramycin was appreciably greater than in those who were given the other two drugs. Indeed, in several instances these manifestations were sufficient to warrant transferring the patients from terramycin to one of the other two antibiotics. This experience with terramycin is somewhat in contrast with the observations of others and may have been dependent upon several factors. In the first place, the Malayan patients were given relatively large doses of terramycin, i.e., a regimen similar to that used with chloramphenicol, and in the second place, early production lots of this antibiotic were employed. Subsequently, more highly purified lots of terramycin were administered by others for research purposes and were distributed commercially.

Each of the therapeutic agents listed in Table 1 has a marked capacity to inhibit the growth of rickettsiae but none is capable of eliminating the rickettsiae from the patient's tissues. Therefore, these drugs are rickettsiostatic, not rickettsiocidal. It is important to remember this point for it has a strong bearing on the method by which the treated patient ultimately recovers from his rickettsial disease and it also bears on the duration of therapy which is required to prevent a relapse.

The specific antibiotics control the manifestations of rickettsial infection by suppressing growth of the agent and enable the patient to cure himself. Thus, eventual recovery in the treated, as well as in the untreated, patient depends upon the development of immunity and the control of the rickettsiae by this mechanism. Patients with scrub

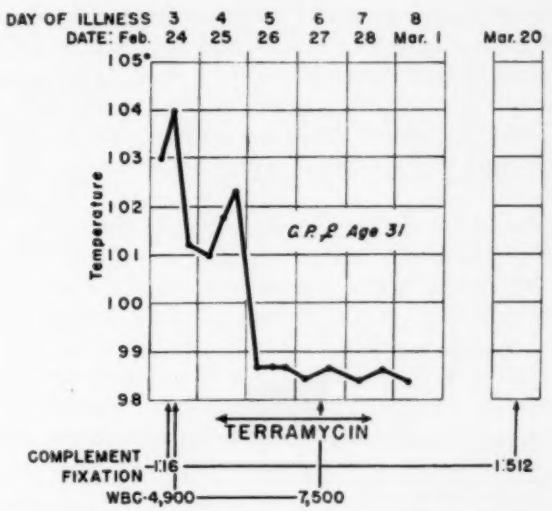

Figure 2—Patient with rickettsialpox who was treated with terramycin. (Reproduced by permission from *Ann. N. Y. Acad. Sci.*, 1950, reference 4.)

typhus who were treated with either chloramphenicol or aureomycin for a period of twenty-four hours were able to suppress the clinical manifestations of their illness for a period of about one week. If immunity had not developed by the time this suppressive effect had begun to diminish, then recrudescence of the disease occurred. Therefore, a proportion of those patients who were treated for a short time within the first few days after onset suffered relapses; incidentally, such relapses were readily controlled, or prevented, by additional therapy. In contrast, patients who were treated during the second week for a similar short period of time did not suffer relapses. These persons were gaining immunity as the suppressive effect of the antibiotic waned, hence, control of the disease passed from one mechanism to the other without a break in continuity and no relapses occurred.

The other rickettsial diseases are benefited about as much by the newer antibiotics as is scrub typhus. Patients with epidemic or murine typhus become afebrile within about two days after therapy is instituted while those with Rocky Mountain spotted fever require approximately three days. Patients with rickettsialpox generally recover promptly and

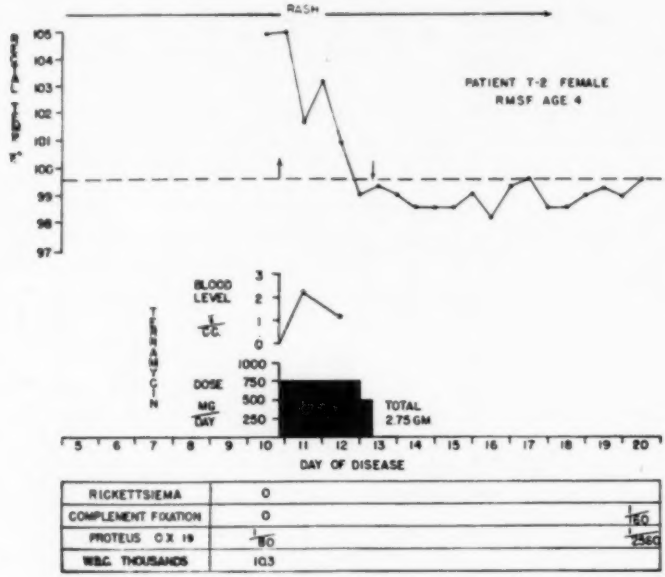

Figure 3—Terramycin in patient with Rocky Mountain spotted fever.
(Reproduced by permission from *Ann. N. Y. Acad. Sci.*, 1950, reference 5.)

patients with Q fever are materially benefited by these therapeutic agents. While there is no need to discuss in detail the use of each of these three antibiotics in these various rickettsial diseases, it is of interest to illustrate certain of the clinical results obtained in several of them with the newest member of the group, namely, terramycin.

Figure 2 illustrates the prompt therapeutic response obtained in a patient with rickettsialpox who was treated with terramycin. This woman was cared for by Dr. Harry Rose and the graph is taken from one of his recent publications.[4]

Figure 3 summarizes the results obtained in one of Dr. Woodward's patients who received terramycin for the treatment of Rocky Mountain spotted fever.[5] The chart is essentially identical with earlier ones which portrayed the effect of chloramphenicol and aureomycin on patients with this disease.

The physician who has either chloramphenicol, aureomycin, or terramycin can treat the rickettsial diseases of man and expect to get

dramatic and gratifying results. Our experience has led us to prefer these three in the order just listed. However, that is the opinion of one group and others, for example, Ruiz Sanchez in Mexico, prefer aureomycin to chloramphenicol.[6] The truth of the matter is that all three are so efficacious in the rickettsioses that it is rather difficult to choose between them. We are indeed fortunate in having three drugs which are so excellent.

The matter of drug dosage for the rickettsioses is relatively simple. The administration of 3.0 grams orally each day until the patient's temperature is normal is a good general rule to follow. When one uses chloramphenicol, a loading dose of 3.0 grams is usually employed. With aureomycin or terramycin the loading dose is sometimes omitted and the total daily dose may be reduced slightly. There is no real indication for continuing treatment after the patient becomes afebrile; if a recrudescence of disease should occur, another course of drug may be given. There seems to be no evidence of the development of drug resistance which would interfere with the efficacy of the antibotic in the treatment of a rickettsial relapse.

There is no doubt that continuing efforts will be made to discover new drugs and antibiotics which are of value in the treatment of the rickettsial diseases. While this is to be encouraged to some extent, it should be realized that such efforts have much in common with gilding the lily. The recent great advances in the treatment of rickettsial diseases are on a par with the giant forward strides which were taken with the application of the sulfonamides and penicillin to the treatment of bacterial diseases. The one important step which remains in the therapy of rickettsial diseases is the discovery of a truly rickettsiocidal drug which is non-toxic for man. If such were found, it would probably supersede the present rickettsiostatic substances. It is my personal opinion that the advances in the treatment of the rickettsioses have been so great that research efforts can now be diverted from these diseases to the important subject of the therapy of viral diseases.

Now that we are ready to discuss the problem of therapy of viral diseases, I wish that I had the facile adaptability of the Roman mythological figure Janus who could face two ways at the same time. Viruses of psittacosis-lymphogranuloma venereum group are rather closely related to the rickettsiae and are highly susceptible to the new rickettsiostatic agents. When one proceeds from this group to the remaining viral

agents, he arrives on rather insecure ground. In this last segment of the field, laboratory experiments which indicate efficacy of the antibiotics against the viral agents are either lacking or have given conclusively negative results. Hence, in discussing the use of modern therapeutic methods in the treatment of many of the viral diseases, one is dependent upon the evaluation of the clinical response of patients with a disease which is often of variable severity and irregular duration and is frequently complicated by bacterial infection. It need hardly be mentioned that this part of the field is a quagmire which demands cautious treading.

Reports have appeared on only a few patients with psittacosis or ornithosis who have been treated with chloramphenicol or aureomycin. The results in these instances were as encouraging as one would have anticipated on the basis of the excellent therapeutic effects of these antibiotics in experimental infections with psittacosis viruses. Aureomycin and chloramphenicol appear to be of considerable value in the treatment of patients infected with the virus of lymphogranuloma venereum. Furthermore, the evidence to date suggests that these antibiotics are superior to the sulfa drugs. It is worth noting that the recent reports of Greenblatt[7] and others have confirmed the initial studies of Wright and Sanders[8] regarding the marked and rapid improvement of lymphogranulomatous proctitis following therapy. The workers in Georgia[7] are not as enthusiastic as earlier investigators on the subject of relief of the bubonic form of lymphogranuloma venereum; furthermore, they are of the opinion that aureomycin is somewhat superior to chloramphenicol for treating this disease.

The viruses which cause trachoma and inclusion blennorrhea have certain points in common with members of the psittacosis-lymphogranuloma venereum group; these include similar morphological properties as well as susceptibility to the sulfonamides. Both aureomycin and chloramphenicol have been reported to be of great value in the treatment of these infections of the eye. Freyche[9] in an excellent recent summary of the treatment of trachoma concludes: "aureomycin and chloramphenicol . . . on both theoretical . . . and practical . . . grounds may constitute the specific therapeutic agent or agents for this disease." It may be noted that in most cases reported to date (and these are less than 100), the antibiotics have been applied locally to the eye. However, in the few patients who have received aureomycin systemically and in the

somewhat large number who have received chloramphenicol by mouth[10] the results have been sufficiently gratifying to warrant more extensive studies. Investigations on the use of the new antibiotics in the treatment of trachoma are now in progress on a considerable scale in several widely separated geographic areas of the world.

There are a number of virus infections with dermatological manifestations which have been subjected to treatment with chloramphenicol and aureomycin mainly on the grounds that these therapeutic agents might help and would do no harm. These diseases include herpes zoster, extensive involvement with herpes simplex virus, widespread eczema complicated by infection with vaccine virus, molluscum contagiosum and a number of other conditions which bear the impressive nomenclature so dear to the dermatologists. I wish it were possible to give you a simple answer as to whether these therapeutic regimens are worthwhile. Frankly, it is impossible to evaluate the reports at this time. It is well to remember that the newer antibiotics are potent antibacterial agents active against a wide variety of micro-organisms; the antibacterial effects may have contributed to the improvement in the patient's condition which was attributed to the therapy. While it is not possible on scientific grounds to approve the use of aureomycin, chloramphenicol, terramycin, or penicillin in these dermatological infections of viral origin, nevertheless, as a physician I feel justified in employing one or another for at least a few days. If no benefit is derived within this period, then one may abandon the antibiotics with a clear conscience.

A considerable number of reports have appeared on the treatment of primary atypical pneumonia and of influenza of either the pure viral type or complicated by pneumonia. Most of these have recorded rather prompt improvement in the patient's condition. In the viral infections of the pulmonary tissue, as in the viral infections of the skin, it is extremely difficult to divorce the viral and bacterial elements and, as a corollary, it is almost impossible to decide whether the beneficial effects attributed to the newer antibiotics were dependent upon their antibacterial effect or their action on the viral agent. Aureomycin, chloramphenicol and terramycin are of great value in the treatment of bacterial pneumonia. Too often the diagnosis of primary atypical pneumonia is made on no grounds other than the fact that the patient with pulmonary consolidation fails to respond promptly to penicillin therapy. It could be that many of the instances in which the three new anti-

biotics succeeded when penicillin failed were dependent upon their antibacterial effect rather than on the antiviral action. On the other hand, there are a number of groups of investigators who have considered these newer antibiotics to be valuable in the treatment of patients with the usual clinical findings of primary atypical pneumonia associated with a rise in cold agglutinin substances and without conspicuous evidence of bacterial infection.[11] The physician who sees such patients is justified in employing therapeutic amounts of the newer antibiotics. However, if the selected drug does not elicit definite improvement within two days, there is little indication for continuing it.

The problem of the therapy of influenza is perhaps more difficult to evaluate than that of atypical pneumonia. The simple viral infection without pulmonary consolidation, as generally seen in recent years, is a relatively mild disease which requires only rest and symptomatic therapy. Those patients who develop pulmonary consolidation surely warrant treatment with the antibacterial substances. It may be mentioned in passing that none of the chemotherapeutic or antibiotic agents now available have any appreciable activity against influenza viruses in experimental animals.

In this connection it is worth-while bringing to your attention the experience with influenza in the Canadian Arctic last year. On Victoria Island, fatal influenza, resembling that seen in the last great pandemic, attacked a number of small isolated groups of Eskimos.[12] Some sixteen deaths occurred among the ninety Eskimos, all of whom contracted the disease, before a medical team was flown in to care for the patients. With the arrival of the team, practically all patients were treated with penicillin and the fatalities ceased abruptly, although a number of the patients had pneumonia when therapy was instituted. Subsequent studies on the viruses which were isolated from one of the fatal cases as well as from several survivors showed that the strains of virus were essentially identical with certain of the influenza A and A prime strains which had caused mild disease in more populated areas within recent years.[13] It would appear that this Arctic experience demonstrated the importance of modern chemotherapy in controlling the bacterial element in fatal cases of epidemic influenza. It is not too much to hope that this observation in the Arctic may provide a preview of the usefulness of the antibiotics in preventing deaths in the next pandemic of influenza if or when it occurs.

In summary, the treatment of rickettsial diseases has been revolutionized within the past several years by the introduction of the highly specific rickettsiostatic antibiotics chloramphenicol, aureomycin and terramycin. These same antibiotics possess specific activity against viruses of the psittacosis-lymphogranuloma venereum group which are not too distantly related to the rickettsiae. Practically all of the other viral agents which have been studied in the laboratory are unaffected by the chemotherapeutic and antibiotic agents which are now available. While the human diseases caused by certain of these viruses appear to be benefited by antibiotics, it is difficult to evaluate these results. In a number of such instances, however, the use of the antibiotics is warranted, even though the academic question of their mode of action remains unanswered.

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ADVANCES IN THE TREATMENT OF CHRONIC ALCOHOLISM*

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IN trying to evaluate the claims of the efficacy of therapeutic results of chronic alcoholism, one becomes aware of the lack of agreement on definition. There is a persistent tendency to consider chronic alcoholism an entity like a well defined disease instead of a syndrome which may occur in different pathological settings. This fact and its relationship to treatment becomes obvious if one studies even a small number of patients. The findings which I shall use for this special aspect of the discussion are based on a broad and intensive study of patients of the Payne Whitney Clinic, carried out by Mary J. Sherfey.

The definition which our group and many other groups have used for fifteen to twenty-five years is the following: a patient suffers from chronic alcoholism if he uses alcohol to such an extent that it interferes with a successful life (including physical, personality and social aspects), and he is either not able to recognize this effect, or is not able to control his alcohol consumption although he knows its disastrous results. This takes into consideration undesirable effects on physical and mental health, on family and group relationships, on work and other responsibilities.

Chronic alcoholism does not depend on alcohol consumption as such but on its relationship to individual susceptibility. There is no indication that one deals with an addiction as addiction is usually defined, because tolerance and definite withdrawal symptoms do not develop. Acute intoxication and the individual's reaction to it do not give us the picture of chronic alcoholism although they occur in this setting but also without it. It is important that we try to distinguish the chronic alcoholic from the excessive and the heavy social drinker. An excessive drinker is an individual who uses alcohol frequently and in large quantities and may even behave pathologically when under the influence of alcohol.

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He is, however, capable of overcoming the habit when he becomes aware of the necessity for it. A heavy social drinker drinks heavily during social occasions, with frequent or even regular intoxication, but the drinking does not present a serious handicap. The excessive and the heavy social drinker are amenable to medical advice if they can recognize its importance. There is no special psychotherapy necessary to have such a patient change his mode of living if one can present sound arguments to him. If he is unable to accept or to follow through the necessary consequences, then, by definition, he must be considered a chronic alcoholic and be treated as such.

In the treatment of chronic alcoholism, of the etiology of which little is known, the physiological, social and psychopathological setting must be considered. From Dr. Sherfey's study we may expect a considerable number of paranoid schizophrenic patients who are heavy drinkers but are considered chronic alcoholics because of their psychopathological behavior. With increased drinking the behavior of these patients becomes increasingly more frankly pathological. An excessive use of alcohol during the psychiatric illness is common among manic and depressed patients; the onset of the psychiatric illness and of excessive drinking usually coincide. In a minority of such patients there is a marked decrease in drinking when the patient recovers. The largest group in Sherfey's study consists of a social and psychoneurotic psychopathic personalities. Chronic alcoholism among epileptic patients is not so frequent as the literature of 30 years ago tried to make us believe. In a relatively small group of patients with brain damage excessive or chronic alcoholism may develop and aggravate the already existing psychopathology. In these patients marked limitation of alcohol consumption must be achieved in order to be able to treat the underlying personality disorder. It is obvious that there is always considerable danger that physicians and patients take the exacerbation of drinking which starts during a psychiatric illness too lightly, and expect spontaneous reduction of alcohol consumption with improvement of the psychiatric illness. Such optimism is not justified. It is not unusual that after the improvement of a depressive illness or an anxiety neurosis a previously excessive drinker may have become a chronic alcoholic.

About a third of the chronic alcoholic patients in Dr. Sherfey's group did not suffer from a well-defined psychiatric illness. They might be considered rigid, even somewhat compulsive personalities or persons

who had not developed sufficient self-reliance. In my own group I also have patients who were well adjusted individuals until after the age of forty and then, in connection with prolonged life strain, developed from social drinkers into chronic alcoholics.

These observations are important for our therapeutic considerations. They emphasize the fact that treatment must be individualized. We know that all these patients have a dependence on alcohol but we do not know what the essential features of this dependence are. To argue that all these patients have a similar type of personality or that they are all psychopathic or psychoneurotic personalities simplifies the problem far too much. The success of a therapeutic procedure must be as carefully analyzed as the failures. Indications as well as contraindications for therapy are important.

Chronic alcoholism is a biosocial problem and never merely a physical or psychologic-psychopathologic or social phenomenon. In treatment all these aspects must be considered, and one must seek to modify existing strains on the patient in every one of these fields. Even if isolated factors are found to be of importance, they can never wholly explain chronic alcoholism. Their removal would rarely lead to a lasting recovery, unless the patients spontaneously made other adjustments. Of the special dynamic factors or developments which in the past have been made the center of therapy I might mention sexual maladjustments (especially latent homosexuality), infantile fixations, compulsive factors, social influences, and constitutional or acquired metabolic or hormonal factors. Clinical studies failed to establish a general importance of any of these factors. A sound scepticism, accompanied by a desire and need for therapeutic activities, has become obvious in recent years and is a most encouraging basis for advances in treatment of chronic alcoholism. Therapeutic procedures are often uncritically applied but nevertheless frequently surprisingly good results are obtained which must be critically surveyed. In recent years, the treatment of chronic alcoholism has become a part of medicine which wishes to use the knowledge, helpfulness and skills of all branches of medical and social science.

Psychotherapy is the main tool for the adjustment of the individual. The main stress is now put on the analysis of the whole personality. Special factors, e.g., latent homosexuality or oral factors receive attention but are not made the main issue. Increasing attention is directed to emotional strain and in what way and to what extent alcohol relieves this

strain. A serious therapeutic problem in alcoholic patients is their difficulty in becoming aware of their emotions. In psychotherapy emotions guide the physician. They direct the patient's and physician's attention to specific underlying dynamic factors. These factors may have been disregarded or repressed by the patient. The emotions permit their recognition or open possibilities to bring them forth and study them. In those patients unable to recognize or admit their emotions, the psychotherapist is handicapped severely. Attempts are therefore made to obtain an understanding through the use of projective techniques, e.g., the Rorschach experiment and the Thematic Aperception Test. Thus far, the therapeutic usefulness of these tests has been limited. Another possible avenue might be through the observation of the physiologic expression of emotions. There are promising leads in this field although they are not far enough advanced to be of general practical importance. The analysis of dreams and symbolic acts is a procedure which may be helpful in the total psychotherapy.

At present, psychotherapy of chronic alcoholism focuses more on an understanding of the individual personality than of unconscious motivations. The goal is to determine the factors which produce stress, and how they can be recognized so that the patient may avoid, or minimize, stress.

In patients whose alcoholism is part of a well-defined psychoneurosis or of psychoneurotic personality changes, intensive analysis of the dynamic factors and life development is needed. Accordingly, good results may be obtained by prolonged psychoanalysis or by other types of analysis.

Group psychotherapy has been tried in a limited extent. In small groups of five to eight patients, a patient may share his psychological and social problems with others and obtain emotional relief as well as a better perspective. Participating in recurrent group meetings, he will develop a positive relationship to the other participants and lay the foundation for social integration.

The role of interpersonal factors is fully recognized and constantly taken into consideration. In all alcoholic patients we deal with a social maladaptation. These patients have difficulty in belonging to groups.

In alcoholism the study of other members of the family is more important than in the treatment of a psychoneurotic illness. Frequently a social worker may be helpful in obtaining additional information, by offering psychological support to the marital partner, and by helping

members of the family to modify their attitudes to the patient and his drinking. A social worker may have to form an active therapeutic team with the psychiatrist. In order to be able to function well, she must understand the problem of chronic alcoholism with all its implications. It is a frequent observation that the alcoholic needs help and guidance in the development of satisfactory social recreation. Unfortunately, our present way of living makes it difficult to find solutions of lasting value. Some of the current attempts will be discussed later.

Progress has been made through an understanding and correction of dietary deficiencies. These deficiencies are not contributory to the chronic alcoholism as such, but lead to serious secondary complications which have become increasingly less frequent. In general, alcoholics are in a better physical condition than fifteen years ago. When physical complications are present, especially dietary deficiencies, the physician is able to correct them. The frequency of liver involvements is disputed, but considered less serious than previously. The control of infection, now possible, prevents the dreaded complications of the past. Progress in anesthesia makes operative procedures less troublesome. Dehydration and loss of blood can be corrected. It can be stated that advances in internal medicine permit the physician to be more aggressive in the treatment of chronic alcoholism and to push the patient into an active social adjustment where previously one had to proceed more slowly.

On the other hand, there is no way at present in which the problem of chronic alcoholism can be attacked directly through physiologic and pharmacologic means. It seems possible to clear up alcoholic intoxications rapidly and prevent unpleasant after-effects (hangover) by use of ACTH or adrenocortical hormones. Similar results have been obtained by the oral or intravenous administration of sodium chloride which is administered on the assumption that it elevates a decreased blood chloride level and thus alleviates thirst. Thus, the withholding of alcohol in intoxicated patients who are admitted to a hospital seems to become easy. These therapeutic means are desirable, and may offer new therapeutic opportunities for acute conditions but do not have a direct bearing on the treatment of chronic alcoholism.

The controversy of hospital versus ambulatory treatment is being replaced by seeking indications for the proper type of treatment. It is obvious that one should prefer treatment with utilization of an active,

normal life to that in a hospital. On the other hand, if this can be made possible only by a therapeutic compromise, hospital treatment is indicated.

Ambulatory treatment is difficult at best and presupposes a considerable stability of the patient, a good understanding by the marital partner, a satisfactory social adjustment, an ability to utilize existing recreational facilities and to enjoy leisure, and a work situation which offers potentialities for satisfaction and success. It is not frequent that the physician finds a total situation which includes these constructive factors, and it is therefore not surprising that the results of ambulatory treatment are unsatisfactory. Furthermore, physician and patient may overlook the fact that the alcoholic condition usually presents a far advanced chronic condition when the patient finally seeks help. As a rule, ambulatory treatment cannot be carried out if the patient is unable to abstain from alcohol for intervals of at least several weeks. Frequent heavy drinking, or persistent moderate drinking with occasional exacerbations, interfere with psychotherapy and the accompanying social adjustment. As I shall discuss later, drinking episodes may alleviate intense emotional reactions and prevent their recognition by the physician and patient. The same may happen with the administration of sedatives. Ambulatory treatment is also contraindicated if the patient lacks emotional control or exposes himself to the danger of losing his reputation or employment. Ambulatory treatment is most suitable for the early stages of chronic alcoholism which, however, physician and patient alike have a tendency to minimize and not to treat actively and in a well planned form.

In recent years pharmacologic help has made ambulatory treatment of mild and even advanced cases of chronic alcoholism possible. The Danish investigators, Hald, Jacobsen, and Larsen proposed to use tetraethylthiuramdisulphide to enforce complete abstinence from alcohol in patients who were unable to control themselves. This drug which has become known under the term, "Antabuse," creates a high amount of acetaldehyde in the body when alcohol is consumed. The result is marked, or even extreme, physical discomfort, if, in the presence of the drug in the body, a small amount of ethyl alcohol is consumed. The symptoms are flushing, nausea, anxiousness, rapid fall in blood pressure. The therapeutic technique starts by demonstrating to the patient the unpleasant, and even dangerous, results if he takes even one drink while

under the influence of the drug. This demonstration is administered after the patient has received a thorough physical examination, with special attention to the heart, metabolic and liver disorders. The physical and psychiatric study of a patient while in the hospital 3-4 days varies, so I shall present a procedure which is used in various places.

For the first four days the patient is given daily tetraethylthiuramdisulphide starting with 1.0 to 2.0 gm., reducing the amount to 1.0 gm. and .75 gm. On the fourth day the patient drinks about 40 cc. of whiskey, in order to understand the physiological reaction which will occur with the drinking of alcoholic beverage. The maintenance dosage which the patient will have to take daily varies between .5 and .25 gm. Mild toxic symptoms (feeling tired, listless) indicate the need to reduce the drug. These symptoms may appear after several days and as late as 10 days. The danger of this drug seems to be less great than has been considered previously. As the toxic reaction consists of a state of collapse, due to widespread vasodilation, one wishes the patient to be in a good general physical condition, and would rule out patients who suffer from cardiac or marked liver involvement. It has also been pointed out that a delayed reaction to alcohol occurs, depending on the length of the interval since the last dosage has been taken. Instead of an immediate reaction, there may be a delay of from an hour to an hour and a half. If such a patient assumes that this delayed reaction indicates that the drug is no longer effective, he may take additional alcoholic drinks, and react very strongly later, developing a serious state of shock. These patients require emergency treatment which can be given only in a well-equipped hospital. The milder forms of reaction clear up spontaneously or can be treated well by the physician in charge of the Antabuse treatment. As serious reactions may have to be seen in an emergency station of a hospital, physicians in emergency pavilions should be informed of Antabuse reactions.

Among the complications of this treatment should be mentioned impotency, which may not clear up for several months, and occasional delirious reactions. These reactions present a non-specific confusional illness, the psychopathological symptoms depending on the individual personality reactions. Such exogenic reactions may present schizophrenic, paranoid, and affective coloring.

This type of treatment is indicated in the ambulatory treatment of alcoholic patients who are willing and able to coöperate after the treat-

ment and its dangers have been thoroughly explained. Desirable patients are the insecure, dependent alcoholics and impulsive drinkers. Patients to be excluded are those who are unreliable and unable to obtain sufficient insight into their condition and the need for abstinence. This treatment should always be considered as accessory to psychotherapy, and to efforts at modification of the total life situation.

The treatment with tetraethylthiuramdisulphide is still in an experimental stage. Further clinical and laboratory investigations are needed. Recent studies indicate that acetaldehyde is not produced in high amounts. There are other chemicals known which produce a similar effect, e.g., cyanamide. Thus it is likely that new preparations may be found which may be less dangerous and increase the therapeutic usefulness.

Another attempt to insure abstinence by the fear of the consequence is the establishing of a conditioned aversion to alcohol. These patients receive alcoholic drinks following an injection of emetine hydrochloride. The theory is that by a repeated association of alcohol intake and marked vomiting the patient will develop a response of revulsion to the sight, smell, and especially the taste of alcohol. He will, therefore, be able to maintain abstinence even when under emotional strain or when exposed to social situations which otherwise would lead to drinking. The treatment lasts from thirty to sixty minutes, administered on alternating or successive days. Aversion treatment is combined with psychotherapy while the patient is in the hospital. The whole hospital stay lasts about 10 days during which time four to six treatments are given. Afterwards, the patient will be treated on an ambulatory basis, with limited psychotherapeutic help. After six to twelve months have elapsed, aversion to alcohol is reinforced by one or two treatments with emetine.

A most important aspect of ambulatory treatment has been established through appeal to religious convictions, by religious conversion, and social support. In the last ten years great aid has been offered many patients through an association of former alcoholic patients which is called "Alcoholics Anonymous." Through these former patients who have known the difficulties and guilt reactions of the chronic alcoholic and who have found help in spiritual guidance, the patient may be guided to a similar solution. He will be able to establish sound social relationships, and learn to lead an active life which will increase steadily his belief in himself. His new associates will not only help him to find a practical solution for his life but also be ready to stand by if new

difficulties might stir up the urge to return to drinking. These former patients are urged to be active in helping other alcoholics. This practicing of his belief will strengthen it and give him the satisfaction of doing something worthwhile. The influence of Alcoholics Anonymous has become far reaching and its value is well recognized by the medical profession. The members brought optimism into a field in which most medical practitioners have felt helpless.

Developments similar to those of Alcoholics Anonymous were started sixty years ago in Europe and have maintained a strong influence. These groups consist of total abstainers, with a minority consisting of former alcoholic patients. Their effort is directed toward the support of former patients to prevent relapse and to achieve social reforms which would decrease alcoholism. These groups, the largest and best known of which is the Blue Cross Society, are utilized freely by physicians in the ambulatory treatment of alcoholics. The activity of Blue Cross is especially marked in central Europe and in Scandinavia.

Ambulatory treatment which was previously carried out entirely in the physician's office is directed increasingly in out-patient services. It has been found desirable to have an alcoholic patient admitted for a few days to a general hospital. During this period alcohol is withdrawn immediately, the patient restored to better health by suitable dietary and medical help, based on a thorough physical examination. His personality, life development, and current problems are reviewed and plans for a life adjustment are outlined. During this phase of physical and psychotherapeutic readjustment, in some hospitals, representatives of Alcoholics Anonymous are brought to the patient in order to establish a healthy contact for after discharge from the hospital. After a week to 10 days the patient is able to leave the hospital and receive prolonged treatment in the out-patient service. He will be treated psychotherapeutically in half-hour to one-hour interviews, in the beginning twice a week, and later once a fortnight or a month. These therapeutic sessions attempt to clarify the factors which played a role in the development and in the maintaining of chronic alcoholism. Members of the immediate family are brought into the therapeutic contact in order to give them an understanding of the patient's difficulty, to gain their advice and support and modify undesirable attitudes. The psychologist may offer advice for more suitable occupations. Lay organizations, including churches and Alcoholics Anonymous may be called

upon for strong support and for helping to develop opportunities for socialization and recreation.

Through private initiative and through newly developed state agencies, out-patient treatment has become a strong factor in treatment and rehabilitation of alcoholic patients. There are several types of therapeutic plans; widely used is the Yale Plan. Its essential features are broad educational efforts, including the training of skilled workers in this field, and help through consultative clinics. For intensive therapy the patients are referred to therapeutic clinics.

State commissions have been created in a majority of the states. The function of these commissions varies but definite patterns seem to develop. It is important that these agencies be integrated in state health departments and include in their responsibility therapeutic, research, education, and preventive aspects. Ambulatory as well as hospital treatment should be established and furthered, utilizing psychiatric, general medical, and public health facilities.

Hospital treatment has been utilized insufficiently. There has been an increasing tendency to use general hospitals for help in acute intoxications and for preparation for ambulatory treatment. While previously such treatment has frequently been given haphazardly, well planned treatment is now carried out in some hospitals as I have discussed above. It is very doubtful that a large number of hospital beds need to be reserved for this purpose if treatment is well conceived and followed by ambulatory treatment. If prolonged treatment in a hospital is indicated, even if only one to two months, it should not be carried out in a general hospital. The only exceptions are alcoholic patients who, because of physical complications, need bed rest. Otherwise the alcoholic patient needs a therapeutic routine which includes occupational activities and socialization. The only hospital which offers this type of treatment for the alcoholic is the psychiatric hospital. This does not imply, however, that every psychiatric hospital provides the treatment indicated. At the present time it depends on the attitude as well as on the knowledge of the psychiatric staff whether an alcoholic patient can find help in a psychiatric hospital. If one occupies oneself intensively with such a patient, one finds that he presents a challenging psychodynamic problem. The therapeutic results to be expected are as good as in many other psychiatric and medical problems if one is able to select suitable patients, has reasonable goals, and adjusts the treatment

to the individual case. Most psychiatric hospitals request a year of treatment in order to achieve a readjustment of the personality and reëducation of faulty ways of behavior and living. In such a setting personality analysis may be made the main issue of psychotherapy. In other patients the psychotherapeutic effort may be directed to an analysis of the behavior in the hospital, especially in work and group activities. The length of hospital stay does not seem unusually long if one considers the chronicity of the alcoholism and the length of hospital treatment which is required in the treatment of some physical illnesses, e.g., tuberculosis. The results of long-term psychiatric treatment in a hospital are gratifying. A considerable number of these patients are able to make a success in life, a small number abstaining permanently, a larger number relapsing occasionally but succeeding far better than previously.

In some European countries (especially Switzerland) good results are obtained by the use of farms for alcoholic patients. It is necessary that patients be carefully selected by a psychiatrist who evaluates the patient's psychopathologic condition, his personality assets and his desire for help. It would be ideal to have such patients receive intensive psychotherapy for four to six weeks in a psychiatric hospital prior to admission to the farm. The psychotherapeutic help while the patient lives on the farm can be reduced to a minimum. The advantages of the treatment on therapeutic farms are regular modes of living with responsibilities similar to those in everyday life, living in a group of individuals, utilization of leisure time in evenings and on Sundays. Most important is the feeling of belonging to a group of people, consisting to a large extent of other alcoholic patients, some of them far advanced on the road to recovery, others at the beginning of it. This interesting social constellation is of great therapeutic value. The results of treatment are good. One institution (Ellikon) has reviewed the results over a period of twenty years. It seems that about one-third of the patients have made a good life adjustment. The majority of these patients did, however, not remain complete abstainers after a period of five years had elapsed. About 46 per cent of all the patients treated during those twenty years were not helped for any satisfactory length of time. The best results on these farms are obtained if the patient stays about a year. From a personal study of these farms, I believe that considerably better results than those quoted could be obtained if the patients were selected more carefully after they had been studied in a psychiatric clinic and received

suitable psychotherapy. The low cost of this treatment makes it a feasible attack anywhere. More important is the fact that the patient's self-esteem is steadily strengthened by his ability to contribute through his work to the cost of his treatment.

For many medical, psychiatric, and administrative reasons special hospitals for the long-term treatment of alcoholic patients have been found undesirable.

During the last few years, in conjunction with research work in the etiology of chronic alcoholism, the treatment in the Payne Whitney Clinic has been considerably modified. After 4 weeks of intensive study and psychotherapy during which time the patient is not permitted to leave the hospital, the patient is urged to try himself out by visits to his family or friends, by shopping trips, movies, etc. As soon as sufficient self-reliance has developed the patient is advised to return to his work, or to find new work. During this period of treatment, which may last from several months to a year, the patient lives in the hospital, returning for supper and having one evening during the week and his weekend free for social recreations and visits with his family. The understanding is that the patient carry out complete abstinence from alcohol and sedatives. Each day when returning to the clinic, the urine is tested for alcohol. It is remarkable how rarely these patients consume alcohol. Whenever this occurs the factors leading to drinking are studied with the patient. If it happens more than once the patient is not considered ready yet for an active life and more restricted treatment in the hospital is resumed. Through careful study of the individual drinking pattern of the patient and the role of his drinking with respect to his emotions, it frequently becomes possible to predict impending need for alcohol. By making the patient aware of these observations, it becomes possible to analyze the situation constructively with him and make him practice suitable precautions or restrictions. Many of these patients seem to be essentially lonely—persons who wish to depend on social relationships with others. Returning to the hospital they find this social "belonging." They feel that they can be themselves without fear of criticism or rejection. Through a close relationship with respective members of their families, as well as friends, undesirable relations on the outside can be modified so that the return to the family becomes attractive and successful. Ambulatory treatment after discharge is continued over a period of years, with visits becoming increasingly less frequent.

In connection with the description of this treatment I wish to refer briefly to the related research work. Progress in therapy must depend on increased knowledge, and research in the etiology of alcoholism will have to offer the basis for new kinds of treatment and modifications of current procedures. Applying our knowledge of specific physiological changes occurring in the presence of specific emotions, it became possible to understand emotional states which preceded drinking and were decreased in intensity by drinking. It is a well-known fact that the alcoholic patient usually has considerable difficulty in recognizing his emotions. It is equally difficult for the observer, e.g., the psychiatrist, to recognize them. By studying biochemical changes in the blood it is possible to determine certain emotions as well as their intensity. In our alcoholic patients the most frequent emotional reaction leading to drinking is suppressed resentment which can be determined biochemically by the influence of such blood on the contractions of the intestines of rabbits. The substance found is biochemically not well defined as yet and does not correspond to any known substance. In a smaller group of our patients, anxiety is present and is associated with noradrenaline in the blood as recent experiments of Fleetwood have demonstrated. Tension is another emotion which in other alcoholics mounted before drinking This emotion is accompanied by cholinergic substances in the blood. As it becomes clear in a large number of patients, alcoholic indulgence is predictable and climaxes a gradually developing increase of specific emotions. These laboratory observations are helpful in the treatment of our alcoholic patients.

This review of treatment of chronic alcoholism can close on an optimistic note. It is obvious that progress has been made. The results of various modes of treatment can be determined by long-term follow-up only. There is no treatment which is suitable for every chronic alcoholic. Through individualized treatment the expected goal can be reached in many patients. It may be possible in a relatively small group to reach a goal which consists of self-reliance and good adjustment to the group in which one lives, with a control of one's emotional reactions without resorting to alcohol or drugs. In a large group a goal can be reached which includes different degrees of rehabilitation over a long or short period of time. Through clinical and laboratory investigations of psychopathologic, physiologic and sociologic factors and their relationships to each other, sound progress in therapy can be expected.

NON-ARTICULAR RHEUMATISM*

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A PHYSICIAN who works in a clinic or research unit devoted to the problems of rheumatic diseases cannot help but be impressed with the high incidence and the large variety of rheumatic disorders involving non-articular connective tissue structures. Collectively, this group of clinical entities has been designated *non-articular rheumatism*. It has been the author's experience that approximately one of every 4 patients referred to the physician or clinic specializing in rheumatic diseases, with a diagnosis of "arthritis," does not have joint disease; instead he has a form of non-articular rheumatism. Confusion in the mind of the physician or the patient is not surprising for the major symptoms of each group of disorders are similar, namely, pain and tenderness in region of joints, and stiffness and limitation of movement of joints. But in the non-articular disorders the joints are normal; the symptoms arise from abnormalities affecting chiefly the structures which move them; the joint movement initiates or aggravates the symptoms and for this reason the inexperienced person concludes, erroneously, that the joint itself is diseased; that the patient has arthritis. It is very important that forms of non-articular rheumatism be differentiated from joint disease, for two reasons: the importance to the physician in managing the patient, for appropriate treatment of the two groups differs; and for the patient's sake, the prognosis and significance of the disease to the patient is vastly different depending upon whether or not joints are affected.

The non-articular rheumatic illnesses include a large number of clinical entities (Table I). It must be appreciated that the designation of non-articular rheumatism applies only to those conditions affecting the non-articular connective tissue directly; it does not include the febrile illnesses, particularly infectious diseases in which rheumatic symptoms may be prominent in the prodromal or early clinical stages. Sometimes in illnesses, such as influenza, the patient's first chief complaint

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TABLE I. CLINICAL FORMS OF NON-ARTICULAR RHEUMATISM

Fibrositis, generalized	Periarthritis (para-arthritis)
Fibrositis, localized:	Panniculitis
Painful stiff neck	Herniated subcutaneous fat
"Lumbago"	Reflex neuromuscular dystrophy
Bursitis	"shoulder-hand syndrome"
Tenosynovitis	"Psychogenic rheumatism"
Tendonitis	(rheumatic manifestations of psycho-neurosis)
"Tendon attachment syndrome"	
Fasciitis	

may be back-ache or generalized aching; however, as the disease progresses the rheumatic symptoms lessen or disappear and the clinical problem is recognized to be non-rheumatic.

FIBROSITIS

The commonest form of non-articular rheumatism affects the fibrous connective tissue and consequently has been called "fibrositis." Usually the nature of the fibrous tissue pathology appears not to be inflammatory, hence the term "fibrositis" is incorrect if strictly interpreted. Even so "fibrositis" is the designation commonly used, and this term is employed in the discussion in the American Rheumatism Association Primer.[1]

Non-articular fibrous connective tissue always shares, to a varying degree, in the abnormalities which exist in patients who have rheumatoid arthritis; sometimes the fibrositis is the predominant feature of this illness. Similarly, affection of the connective tissue around osteoarthritic joints accounts for much of the symptomatology of this form of arthritis. Because the chief pathology in these forms of arthritis is in the joints, the non-articular fibrous tissue disorder associated therewith is called "*secondary* fibrositis," or the fibrositis of rheumatoid or osteoarthritis. But the same disorder of non-articular connective tissue frequently occurs without disease of the joints; this clinical entity is called "*primary* fibrositis." Other names for this entity include "myofibrositis," "myalgia" and "muscular rheumatism," the latter term being quite common among the laity. It is this condition, primary fibrositis, to which attention is now directed.

Clinical Manifestations: In order to establish this entity clearly, for there has been much confusion concerning it, the clinical features will

be reviewed first. Primary fibrositis may exist simultaneously and widely scattered in many parts of the body, i.e., generalized fibrositis; or it may be sharply localized. The more disseminated form involves the fascia, tendons, aponeuroses particularly in the back, shoulders, thighs and hands, although all other fibrous tissue may be affected. The clinical pattern of primary fibrositis is quite consistent. Affected persons are usually young or middle-aged adults. The illness may begin acutely and cause very severe pain, but when it is more generalized, the onset is usually insidious and the development gradual so that the disease is commonly a chronic disorder. Aching and stiffness of the neck, the interscapular upper back, the lumbosacral region or the entire back, shoulders and thighs are common early symptoms. Turning, stooping and twisting motions of the back, abduction and rotation at the shoulders and lying on the side are difficult to do and aggravate the symptoms. Often the hands become stiff; movement of the fingers is difficult; the hands feel clumsy, and grasp becomes so weak that objects are dropped and work with the hands becomes difficult or impossible. The patients tend to tire easily and, because of the discomfort and sense of fatigue, they avoid more strenuous physical activities and may follow a schedule of self-imposed, partial invalidism.

An important feature of this syndrome is the rather consistent effect of certain factors upon the symptoms. Pain and stiffness are usually worse after prolonged rest, consequently patients are most uncomfortable in early morning after a night's sleep. Ordinary activities or planned exercises of the affected parts almost invariably limber the patient and relieve aching. Patients feel best in mid-day; at the end of the day fatigue adds to the symptoms; while sitting in the theatre, at cards or at a desk there is usually no discomfort but with activity thereafter there is considerable aching and stiffness. The stiffness which develops in muscles and other connective tissues with rest and in the cold is much like the "jelling" that occurs in gelatine mixtures when they are refrigerated. Dampness, cold, rain and snow usually worsen these phenomena; warmth, dryness and high barometric pressure characteristically relieve, consequently many persons who have fibrositis suffer more in winter and spring and feel better in the summer and early fall.

Physical signs of this disease syndrome are few. Inspection and palpation reveal no connective tissue abnormality except for mild atrophy of muscle when joint motion has been impaired for a long period. There

are never signs of inflammation or other abnormalities at any joints but due to pain and stiffness there may be limitation of movement of some joints. There may be little or no tenderness but at sites of greater trouble there may be moderate, generalized tenderness. Sometimes great tenderness exists at sharply localized regions from which pain radiates through the distribution of fibrous tissue structure. These have been called "trigger points" or "trigger zones" of pain, and "myalgic spots." Earlier writers described "fibrositic nodules," as almond-sized, tender masses of firm, rubbery consistency commonly located in the lower lumbar and sacral region. However, such nodules are often encountered in non-rheumatic individuals, and are considered by most current investigators not to be part of the fibrositic syndrome.

The patient with fibrositis is in good systemic health and does not appear ill. Fever and loss of weight do not occur. The syndrome usually continues for many months or years, with symptoms fluctuating through an undulating course. Frequently there are remissions and recurrences. Seldom is the disease sufficiently severe or persistent to incapacitate the patient. Truly, it is more of a "nuisance" disorder.

Laboratory Observations: Results of usual laboratory tests are characteristically normal. There is no anemia or leukocytosis; the erythrocyte sedimentation rate is normal or only slightly elevated and roentgenograms of joints show no changes in cartilages or bones. Creatinuria has been reported to be somewhat proportional to the symptoms.[2] Electromyographic studies have shown increased irritability of muscles in some cases, but no abnormality in most.[2,3]

Pathology: Early reports contain descriptions of tissue in biopsies of muscle and "fibrositic nodules." Muscle and white fibrous tissue have been described as showing varying amounts of degeneration and atrophy of the fibres, and sometimes small collections of cellular exudate about some of the more abnormal fibres. The "nodules" were described as collections of edematous fibrous tissue, usually in loose, fatty, subcutaneous tissue. Recently many workers have reported studies of the pathology of muscle and other connective tissue as revealing no characteristic tissue change and they consider, instead of their being an anatomic tissue change, that there are chemical or physio-chemical changes in the connective tissue, possibly due to enzymatic disturbances which alter the physiology of the tissues involved.

Etiology: The cause of primary fibrositis is unknown. The same

uncertainties surround the nature of this rheumatic disorder as exist for rheumatoid arthritis. Sometimes infection, trauma, unusual physical activity, fatigue, dampness and cold appear to be "trigger mechanisms" or contributory causes. In most instances the illness seems to originate "out of a clear sky." Inherited fibrous tissue characteristics may set the background for this ailment.

The lack of demonstrable, characteristic, microscopic pathology in the fibrous tissue, the mystery surrounding the etiology, and the different locations of disturbances sometimes included under the category "fibrositis," have made a few conservative rheumatologists object to the concept of fibrositis. Some physicians insist that there is no such disorder and condemn the use of the term "fibrositis," and they ridicule this diagnosis, as well as the physicians who make it. But I direct your attention to the very consistent, clinical pattern of the rheumatic symptoms and dysfunction which characterize fibrositis unassociated with any demonstrable joint disease, and unaccompanied by indications of any inflammatory process or systemic illness. This syndrome differs so much from other forms of rheumatism that it certainly should be differentiated and managed as a distinct entity. *It is this clinical syndrome,* not a cellular pathologic process producing anatomic damages, that makes up the form of rheumatism labeled "fibrositis." Although this term is admittedly poor (its connotation is ambiguous), it serves to designate a distinctly different clinical entity just as well as the terms "rheumatoid," and "osteoarthritis" which, when examined critically are found to be poor terms for the diseases they label, but which terms common usage has long since made acceptable.

The diagnosis "fibrositis" should be restricted to the clinical disorder described. Simply because the etiology and pathologic features of this syndrome are ill-defined, it is not justifiable to diagnose every rheumatic process free of demonstrable joint pathology as "fibrositis." This has been done too often and presents another reason for some physicians objecting to considering fibrositis as being a distinct clinical syndrome.

Difference in conception of fibrositis is noted in the reports concerning the relative incidence of different rheumatic diseases (Table II). The incidence of "fibrositis" is reported much greater in British civilian and military personnel than among Americans. Although Great Britain is the "home of fibrositis," this difference is more likely due to the fact that other forms of non-articular rheumatism were not separated from

TABLE II. RELATIVE INCIDENCE OF "FIBROSITIS" REPORTED IN RECENT YEARS

Author	*Country*	*Status*	*Per Cent*
Fletcher and Lewis-Taning	England	Civilian	45
Schmidt	England	Civilian — miners	42
Boland	U. S.	Army General Hosp.	5
Boland and Corr	U. S.	Army General Hosp.	7
Savage	Gr. Britain	E.T.O. Field Army	52
		(General Hospital)	20
	Scotland	Army depot	70
Copeman	British	Military	70
Kersley	British	Military — Far East	33

this category. In the United States "psychogenic rheumatism" (rheumatic manifestations of psychoneurosis) is separately classified whereas in England it is not. This undoubtedly lowers the frequency of fibrositis statistics from the United States and further emphasizes the wisdom of restriction of use of the designation fibrositis to a definite syndrome.

Diagnosis: A characteristic clinical history, absence of pathologic joint changes, existence of normal systemic health and negative laboratory findings are the basis for the diagnosis of fibrositis. Differentiation from classical rheumatoid or osteoarthritis is not difficult except in early stages when, in some instances, it may be necessary to study the condition carefully and observe the course of the illness for several months before differentiation is clear. Features distinguishing fibrositis from psychogenic rheumatism will be presented hereafter.

Management: Treatment of fibrositis is supportive and symptomatic.

It is usually helpful for the patient to avoid strenuous physical activity and to procure additional rest during the daytime, but it is a mistake to curtail ordinary activity and recreation that is not fatigue-producing. Mild exercise especially after application of heat usually relieves the stiffness and aching; however, prolonged physical activity commonly increases the discomfort. Heat relieves; massage gradually made rather "firm," is usually helpful. Hot packs are helpful for severe localized pain and warm baths are the best means of heating the whole body. Analgesia can be accomplished best by regularly timed doses of acetyl

salicylic acid or one of its derivatives, or by mixtures of non-narcotic analgesics of simple nature.

When trigger points are located, injection with procaine may relieve by breaking the reflex responsible for referred pain. Such injections may be wisely employed several times at three to seven day intervals. Because of the stiffness which characterizes this syndrome, anti-spasmodic drugs such as d-tubocurarine, and 3 ortho-toloxy – 1, 2 – propane-diol (Tolserol) have been tried. Except in acutely painful neck or low back syndromes where muscle spasm is prominent, these anti-spasmodics are of little or no value for the stiffness of fibrositis usually is not due to muscle spasm, as once commonly believed. Roentgen therapy is usually disappointing. "Fibrositic" vaccines, once quite popular, are of no recognizable value and are seldom used. Vitamin E has been recommended for fibrositis and some authors[4] report brilliant results even when used topically.[5] The majority of investigators have found Vitamin E "speculative" or of purely psycho-therapeutic value for fibrositis. Many trials by the author have resulted in failures. Gold salts usually do not help, and are not recommended. Patients with fibrositis should avoid exposure to dampness and cold. Some patients are relieved when in a warm, dry climate.

Because of the noted success in relief of *secondary* fibrositis of rheumatoid arthritis by cortisone or ACTH, it has been considered likely that primary fibrositis would respond readily to these anti-rheumatic hormones. However, prolonged scarcity of these new hormones have prevented sufficient study to clearly define their value in fibrositis. Two patients in our research group responded promptly and completely while doses of cortisone comparable to the average amount used for rheumatoid arthritis were employed for ten to fourteen days but relapse occurred promptly when the hormone was discontinued. A third patient had only about 50 per cent relief from cortisone. Further studies are needed to clarify the position these hormones may have in the management of fibrositis. At present it appears that the dosage requirement will be comparable to that for rheumatoid arthritis and that short use is insufficient. Realizing the mild nature of this disease and the problems associated with the use of these potent hormones, it seems unlikely that their use for fibrositis will prove wise.

Prognosis: Joint deformities and crippling never result from fibrositis. The disease usually subsides or can be controlled by treatment,

although some stubborn cases cause much discomfort for long periods of time. It is important that patients be informed that they have only a mild, "nuisance disease" for they usually fear that they have arthritis which will cripple and incapacitate them if it persists; they are greatly relieved to learn the disease only causes discomfort and temporary difficulty in joint movements. Persistence in a conservative, intelligently planned program of treatment usually gives good results.

Localized and Special Forms of Fibrositis

Fibrous tissue irritation may be localized. The symptoms and dysfunction depend upon the anatomic localization, nature and severity of the abnormalities. Examples of localized fibrositis are the acute, painful, stiff neck or low back (lumbago). Each of these painful, sometimes temporarily incapacitating disorders results from irritation of muscle sheaths, fascia, tendons and ligaments in a portion of the back. Muscle spasm is sometimes severe, hence, anti-spasmodics are more often helpful in this form of fibrositis. Hot fomentations and injections of procaine at the site of the irritation may effect prompt relief. For such severely painful disorders use of codeine or demoral is sometimes justified. Generally, the more acute the onset, and more rapid the development, the more complete and rapid is the resolution of localized fibrositis.

Bursitis: Inflammation of a bursa is a common form of localized fibrositis. Usually the cause cannot be ascertained; occasionally it seems quite clear that the bursitis has been caused by trauma, unusual activity, exposure to dampness or cold, and sometimes by infection. Since bursae exist about all large joints and some small ones, bursitis may occur in many locations. The subacromial, olecranon, ischial, prepatellar and achilles bursae are more commonly affected (Fig. 1). Different from the nature of generalized fibrositis, bursitis is truly an inflammatory process.

One of the most difficult problems of non-articular rheumatism is the "painful shoulder." Fibrositis is much more commonly the cause of shoulder rheumatism than is arthritis. There has been much confusion surrounding the subject of "painful shoulder." To illustrate: Different authors have discussed painful shoulder under the titles bursitis, tendinitis, calcific tendonitis, non-calcific tendonitis, tear of the musculotendinous cuff, "frozen shoulder," periarthritis of shoulder, peritendinous adhesions, adhesive capsulitis, adhesive or obliterative subdeltoid bursitis, calcific bursitis, interstitial fibrosis and occasionally, simply, fibrositis

Fig. 1—Characteristic appearance of acute olecranon bursitis with fluid in the bursal space.

of the shoulder. Some of these conditions can be differentiated with accuracy, sometimes they cannot be; then particularly a general understanding of the problem is of paramount importance.

Bursitis about the shoulder may begin precipitously or insidiously and may be acute or chronic with respect to severity and duration. Acute subacromial bursitis (the commonest form of bursitis about the shoulder) may be mild or severe. It is characterized by pain and tenderness localized to subacromial region although it may be more diffuse, and intensified near the humeral insertion of the deltoid. The discomfort is made worse when the arm is hanging unsupported, by pressure over the tip of the shoulder or by movement, especially in abduction and external rotation. Many times these motions are markedly restricted by pain. Fluid may distend the bursal sac and thus add to the pain. This fluid may contain calcium salt in semi-solid consistency.

Because of the proximity of the structures, it is difficult in some cases to determine whether subacromial bursitis or supraspinatous tendinitis is responsible for the symptoms. Irritation of one may secondarily affect the other adjacent tissue so that both may cause the pain simultaneously. Calcific deposits in the tendon near its insertion into the greater tuberosity of the humerus is common, and rupture into the bursa may occur. Abnormal calcium deposits may be absorbed or withdrawn surgically, or remain and become firm, even bony hard, and add to the irritation of adjacent structures so as to account for a chronic painful shoulder which may be very stubborn in response to all non-surgical treatment.

Diagnosis is usually not difficult when the clinical pattern is appreciated. Roentgenograms are negative except for the evidence of abnormal, soft-tissue calcific deposits when they exist.

Treatment should be directed to relieve pain and to maintain function; reassurance should be given that the disorder is localized and comparatively mild. Radiant heat or diathermy may relieve, but sometimes aggravate the pain; then cold applications usually relieve. Rest of the shoulder is advisable during the acute phase; graded exercises to restore motion should be instituted as soon as pain lessens. If the bursal sac is distended, removal of the exudate by syringe, or simply puncturing the sac and allowing the fluid to escape into the surrounding tissue may relieve greatly. Infiltration of the inflamed tissue with procaine may relieve sufficiently to warrant repeated injections. Procaine block of the superior cervical ganglion or brachial plexus will give temporary relief and allow exercise of the shoulder so as to avoid stiffness. Roentgen therapy wisely used in small amounts helps some cases, especially in the subacute stage, with or without calcific deposits. Extensive roentgen irradiation should be avoided. If firm calcific masses persist, excision of the calcium deposit and liberation of the adhesive disorder may be required.

Proper treatment provided promptly and persistently usually relieves discomfort until the inflammation subsides. If the condition becomes chronic, periarticular fibrositis may result and cause stiffness of the shoulder. Periarthritis may occur at the shoulder without initial bursitis. If stiffness of the shoulder persists, muscles atrophy and periarticular adhesions form, and gleno-humeral motion may be lost, a "frozen shoulder" resulting. Careful manipulation of the shoulder while anes-

Fig. 2—Palmar fasciitis; note the general flexion deformities of the fingers and the puckering of the palm.

thetized may help to mobilize such a stiff shoulder. Bursitis about other joints produces similar problems; the anatomic localization accounts for the differences in the clinical picture and therapeutic considerations.

Another form of fibrositis involves the tendons primarily. Tendons may become inflamed, although more often they are painful without evidence of inflammation, accounting for the symptom complex known as "tendon attachment syndrome." This may be caused by trauma or by unusual activity and may occur with or without regional bursitis. This difficulty located at the attachment of the conjoined tendon onto the

humeral epicondyle is known as "tennis elbow." Treatment is similar to that for bursitis.

Tenosynovitis: Specific infection, such as tuberculosis may cause inflammation of tendon sheaths; more often cause for tenosynovitis is unknown; sometimes nodular and stenosing changes develop in tendon sheaths so as to impede motion of the encased tendon (DeQuervain's disease). When this condition affects flexor tendon sheaths of a finger, after the finger is flexed, extension may not be possible except with assistance. This condition is called "trigger finger." If warm baths or paraffin dips and exercise do not relieve, incision of the tendon sheaths may be required to free the motion.

Fasciitis and Panniculitis: Generalized inflammation of fascia in the palms of the hands may limit extension of all fingers (Fig. 2). Involvement may be localized to the fascia and tendons to the fourth and fifth digits, producing "Dupuytren's contracture."

Subcutaneous fascia may become inflamed with or without the adjacent fat components resulting in painful nodular subcutaneous swellings. These frequently occur over the abdomen, shoulders and thighs, giving rise to the painful syndrome called "panniculitis."

Herniation of subcutaneous fat through a weak portion of the fascia or a small foramen (recently described as "herniated fat") may occur in the low back and cause pain simulating fibrositis. Copeman and Ackerman[6] dissected the backs of 14 soldiers who died of various causes and found a "basic fat pattern" which coincided with the regions in which what was thought to be "fibrositic pain" and nodules had occurred during life. Instead of subcutaneous ("fibrositic") nodules, small herniations of lobulated fat were found penetrating through fascial tears or through the unprotected foramina by which the posterior primary rami of the first three lumbar nerves pierce the deep fascia. Pain was ascribed to edema in the lobules producing tension which would cause herniation if fascial walls were deficient. At necropsy, fat in the lumbar region could be caused to herniate when pressure was applied to adjacent tissue. Herniations during life were attributed to incidents such as sudden trauma, quick flexion of back, and prolonged rest in the supine position.

Tender subcutaneous "nodules" were removed surgically from patients with back pain and proved to be herniated fat showing no evidence of inflammation. Such herniated fat was believed to be the

"trigger point" of pain in some cases resembling fibrositis. Later cases were treated more conservatively. The overlying skin was anesthetized, the nodule transfixed with a cutting needle from which 10 to 20 cc. procaine solution were injected; then the needle was swept around to undercut the nodule thereby dispersing the edema and tension. Pain and tenderness were reported to be relieved. Since this first report of Copeman others have reported similarly.

Shoulder-Hand Syndrome: This interesting and incompletely understood form of non-articular rheumatism may follow myocardial infarction or other painful intrathoracic lesions, cerebral vascular accidents, irritative lesions in the neck or upper extremity, and sometimes exists without recognizable cause. It is characterized by pain in the shoulder or hand, commonly in both parts; it may be unilateral or bilateral. Shoulder motion becomes limited and the affected hand becomes edematous and painful so that it is held stiff. After several weeks, atrophy occurs in the shoulder and hand and adhesions or contractures limit motion in the affected parts. Severe osteoporosis characterizes the roentgenograms which always show normal joint structure.

This syndrome is thought to be a reflex dystrophy. It is important that it be differentiated from rheumatoid arthritis. Treatment with usual physical measures and analgesics commonly fails. Procaine block of the brachial plexus or superior cervical ganglion is usually an effective means of temporarily allaying pain, which should be accomplished early in the illness, so that functional exercises can be performed to prevent stiffness. If stiffness of shoulder and/or hand results, rehabilitation depends upon persistent physical and occupational therapy.

The effects of cortisone and ACTH are being studied in this syndrome and these hormones may prove valuable at least in some cases.

Psychogenic Rheumatism: A common form of non-articular rheumatism in civilian as well as military practice is "psychogenic rheumatism" —the rheumatic manifestations of psychoneurosis. During World War II it was the commonest form of rheumatism encountered in many hospitals and field areas.[7] Psychoneurotic persons in emotional conflict caused by psychic trauma, fear, anxiety, apprehension or sorrow may experience arthralgia, muscle and tendon pain, stiffness and interference with joint motion resembling common forms of arthritis or fibrositis. The true nature of this condition must be recognized; this is usually not difficult when psychogenic rheumatism exists alone. Absence of joint

changes on clinical and roentgenologic examination, normal laboratory observations, and good organic health are characteristic. Bizarre deformities not conforming to anatomic changes and recognition of other evidence of psychoneurosis are helpful diagnostic features. It may be difficult to differentiate psychogenic rheumatism from fibrositis. In the patient with psychogenic rheumatism commonly symptoms are not localized or consistent. There is lack of benefit from analgesics, and physical therapy and failure to improve in warm atmosphere and after mild exercise—all usually found in patients with fibrositis. Treatment should be directed to relieving emotional conflict and rationalization of the problems. Unless these objectives are realized results will be disappointing.

Summary

About one out of every four persons attending arthritis clinics in the United States does not have arthritis, but has a form of rheumatism affecting only non-articular fibrous connective tissue. Symptoms of non-articular rheumatism are identical with or very similar to those of some forms of arthritis. There are many different clinical varieties of non-articular rheumatism. It is important to differentiate non-articular rheumatism from arthritis, and to ascertain which type of non-articular rheumatism exists, for the proper treatment and prognosis differ.

Usually non-articular rheumatism is only a "nuisance disorder" and proper management gives satisfactory results. The patient should be reassured that the disease is not arthritis, that it is usually mild, and although oftentimes slow to improve, the prognosis is good.

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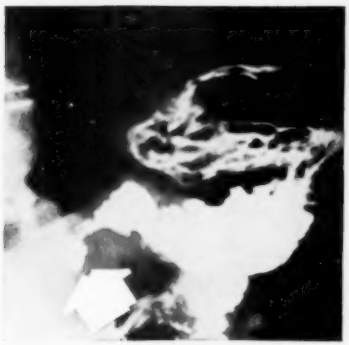

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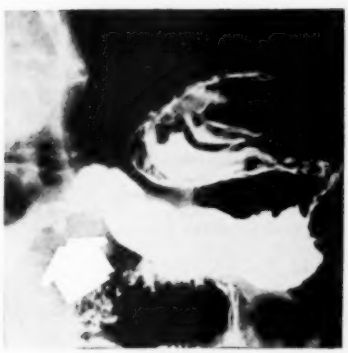

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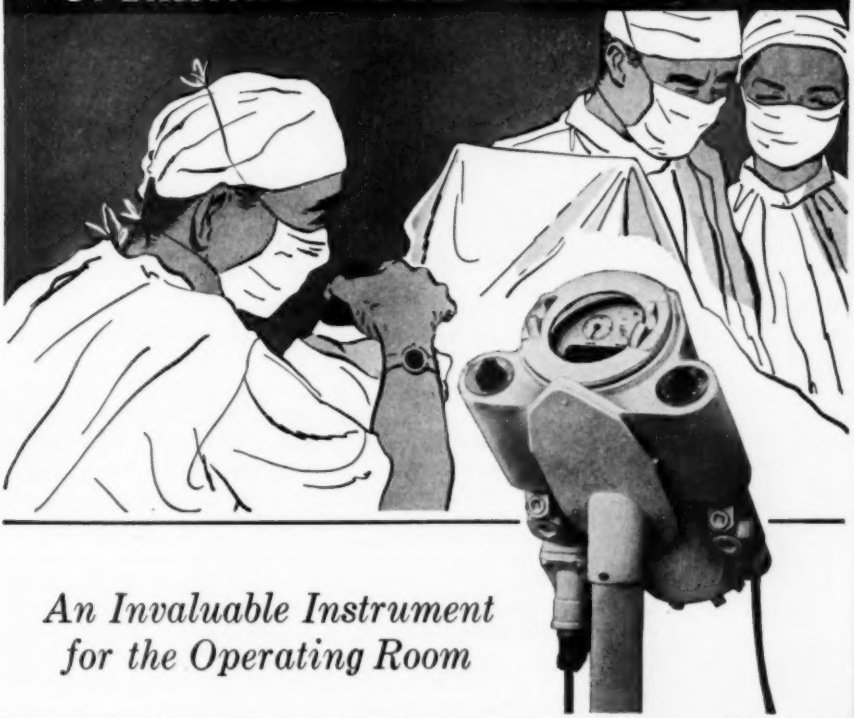

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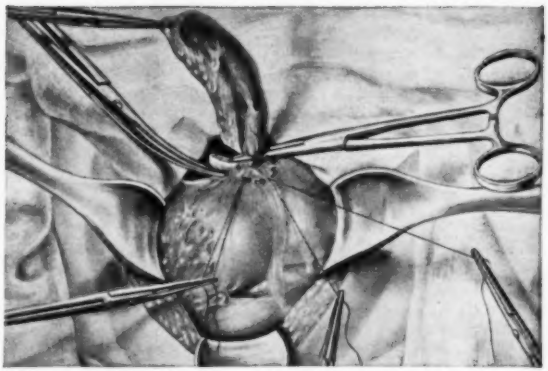

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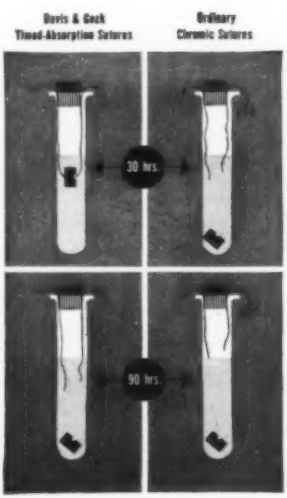

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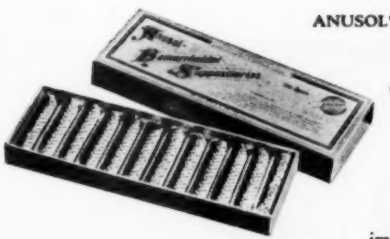

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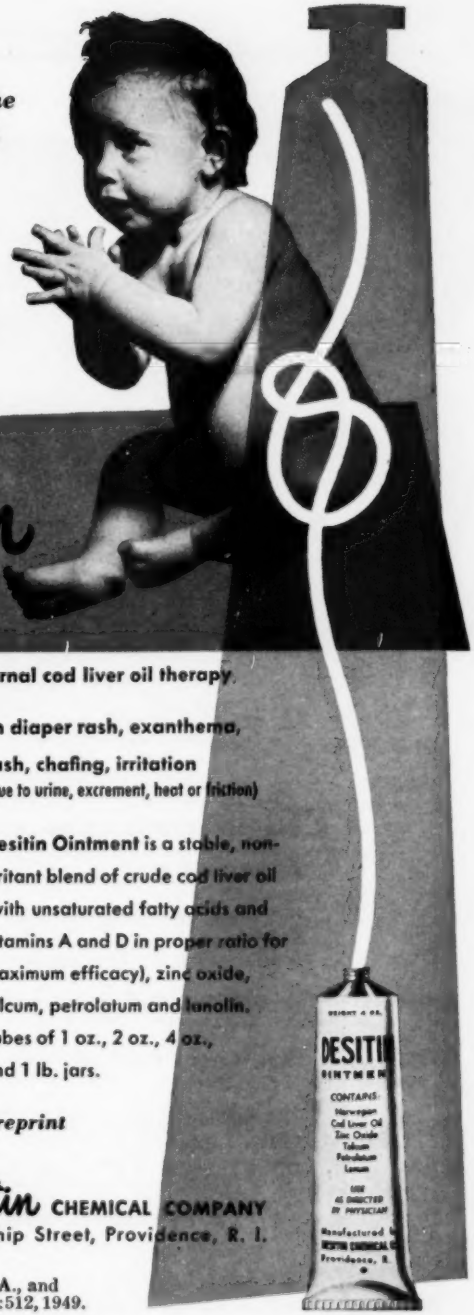

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VIEWS of the Academy building, exterior and interior, have recently been put on postcards. Besides an over-all representation of the 103rd Street facade, the pictures show the main entrance, the reading-rooms, the Rare Book Room, and details of the interior architecture. The building, an unusaully fine example of Renaissance ideas, was erected in 1926. The postcards are available from the Academy Library, 2 East 103 Street, New York 29, at five cents each, or thirty cents for a set of nine cards.

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Armbrust, C. A., Jr., and Levine, S. A.: Am.J.M.Sc. 220:127	"About 60% of the cases showed improvement; i.e., used fewer nitroglycerin tablets, had fewer and milder attacks of pain and could walk greater distances."
Rosenman, R. H., et al.: J.A.M.A. 143:160	"Of 14 patients with angina pectoris treated with [Eskel] . . . a good response was obtained in 11, moderate improvement in 1 and no effect in 2."
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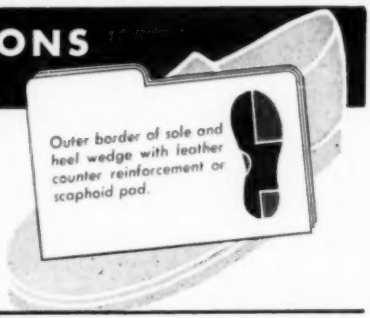

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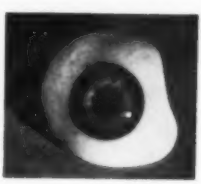
EFFECTS OF FRONTAL-LOBE INTERFERENCE IN ANIMALS AND MAN
NOLAN D. C. LEWIS, *Director, New York State Psychiatric Institute*

APRIL 20, 1951
RELATION BETWEEN SERUM LIPIDS AND ARTERIOSCLEROSIS
FORREST E. KENDALL, *Associate Professor of Biochemistry, College of Physicians and Surgeons, Columbia University; Research Associate, Goldwater Memorial Hospital*

APRIL 27, 1951
THE ETIOLOGY, RECOGNITION AND MANAGEMENT OF ANGINAL HEART FAILURE
H. M. MARVIN, *Associate Clinical Professor of Medicine, Yale University School of Medicine*



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*Perloff, W. H.: Am. J. Obst. & Gynec. 58: 684 (Oct.) 1949.

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1. Hamblen, E. C.: Endocrinology of Woman. Springfield, Ill., Charles C Thomas, 1945; p. 468.
2. Gillman, J.: J. Clin. Endocrinol. 2: 157 (1942).

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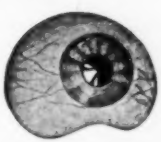

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1. May, C. D., et al.: *Am. J. Dis. Child.* 80:191, 1950.
2. Recommended Daily Dietary Allowances, Rev. 1948, Food and Nutrition Board, National Research Council.
3. Zuelzer, W. W., and Ogden, F. N.: *Am. J. Dis. Child.* 71:211, 1946.
4. Gardner, L. I., Butler, A. M., et al.: *Pediatrics* 5:228, 1950.
5. Nesbit, H. T.: *Texas State J. M.* 38:551, 1943.

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1. Fouley, G. B., Freeman, S., Ivy, A. C., Atkinson, A. J., and Wigodsky, H. S.: Arch. Int. Med. 67:653, 1941.
2. Upham, R., and Chaikin, N. W.: Rev. Gastroenterol. 10:287, 1943.
3. Collins, E. N.: J.A.M.A. 127:890, 1945.

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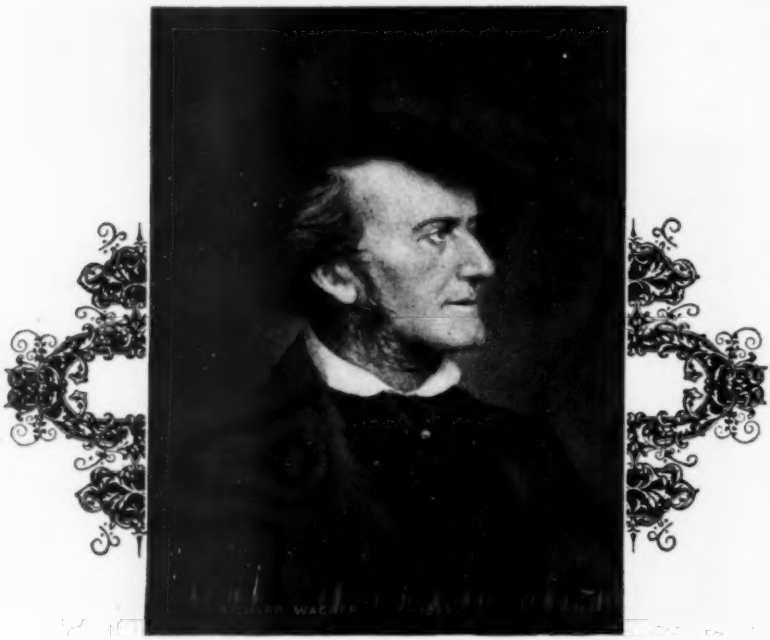

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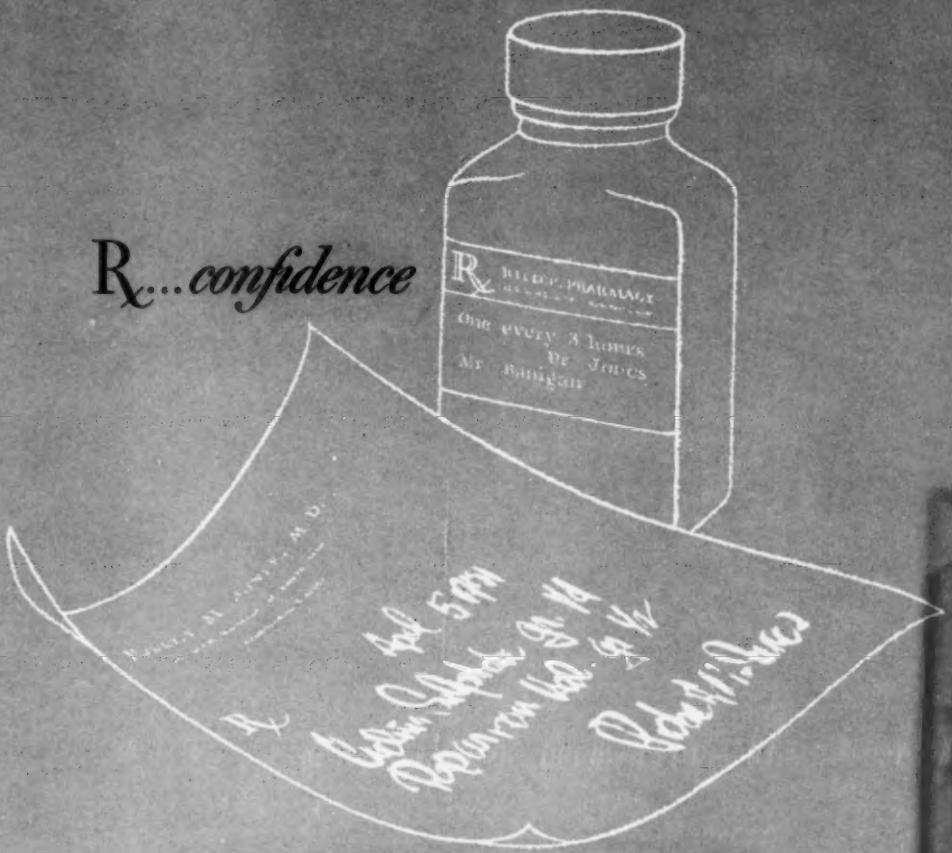

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—Morrison, L. M. and Gonzales, W. F.: Am. Heart J., 38:471 (Sept. 1949).

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